Universidad de Alcalá

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Título de la Tesis

Uso Racional de Antibióticos en Infecciones del Tracto Respiratorio Superior en el Primer Nivel de Atención en Salud en el Ecuador

Tesis Doctoral presentada por

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«Si no conozco una cosa, la investigaré».
Louis Pasteur.

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Abreviaturas

IRAs	Infección del trato respiratorio superior / infecciones respiratorias altas
CAP	Conocimientos, actitudes y prácticas
MSP	Ministerio de Salud Pública del Ecuador
I$	Dólares internacionales
GPC	Guía de práctica clínica
OMS	Organización Mundial de la Salud
EEUU	Estados Unidos de Norte América
LIC/MIC	Países de bajos y medianos ingresos económicos (low and midle income countries)
CDC	Centro de Control y Prevención de Enfermedades
NICE	Instituto Nacional de Salud y Excelencia Clínica
SNS	Sistema Nacional de Salud
IESS	Instituto Ecuatoriano de Seguridad Social
ISSFA	Instituto de Seguridad Social de las Fuerzas Armadas
ISSPOL	Instituto de Seguridad Social de la Policía
CEISH	Comité de Ética de la Investigación en Seres Humanos

Resumen

Antecedente: La prescripción inadecuada de medicamentos es un problema de salud pública que afecta a los sistemas de salud. Los antibióticos son los medicamentos más prescritos en atención primaria y las infecciones del tracto respiratorio superior (IRAs) son las patologías más comúnmente atendidas en el primer nivel de atención en salud. El tratamiento de las IRAs generalmente no requiere el uso de antibióticos; sin embargo, son prescritos ampliamente de forma inapropiada. Por lo anteriormente mencionado, es necesario explorar la situación actual del uso racional de antibióticos en IRAs en Ecuador y determinar cuáles son los factores relacionados y las posibles estrategias para mitigar este problema de salud pública.

Objetivos: Evaluar la situación actual del uso racional de antibióticos en infecciones del tracto respiratorio superior en el primer nivel de atención en salud del Ecuador.

Métodos: Para alcanzar el desarrollo adecuado de la investigación en planteó una metodología en tres fases: *1)* Se desarrolló un estudio no experimental, transversal de tipo analítico para identificar una línea de base del problema de uso de antibióticos en IRAs en el primer nivel de atención en Ecuador, con el propósito de identificar la proporción de prescripción antibiótica y la proporción de prescripción apropiada e inapropiada de antibióticos; por otro lado, se realizó un estudio de costo de enfermedad a fin de identificar el consumo de recursos y el costo sanitario de la atención en IRA en el primer nivel de salud. *2)* Se exploró los factores intrínsecos que motivan la prescripción antibiótica en los médicos de atención primaria a través de un estudio no experimental, transversal de tipo analítico para identificar los conocimientos, actitudes y prácticas (CAP) en relación con la prescripción antibiótica en IRAs; así mismo, se exploró el efecto que tiene un programa de educación en postgrado en atención primaria, en los CAP de los médicos. *3)* Finalmente, se desarrolló un estudio cuasi-experimental, que evaluó el efecto a corto y largo plazo de una intervención multifacética en los prescriptores de un servicio de atención ambulatoria, a través de la implementación de una guía de práctica clínica orientada a la disminución de la prescripción antibiótica en IRAs.

Resultados: La proporción de prescripción antibiótica en IRAs en el primer nivel de atención en salud fue de 37.5%, la proporción de prescripción antibiótica apropiada e inapropiada fueron del 9.75% y 90.75%, respectivamente; los médicos generales recién graduados prescriben cuatro veces más antibióticos comparados con médicos especialistas en medicina familiar OR: 4.62 (95%IC, 2.00-10.67, $p<0.0001$). El costo médico directo para el Ministerio de Salud Pública del Ecuador (MSP) para un episodio de IRAs en niños en el año 2017 fue de I$ 37,28, y el costo total en el mismo año se estimó en I$ 50,478 millones, las consultas de seguimiento y la prescripción de medicamentos representan un componente importante en los costos por IRAs. La relación de proporción para conocimientos inadecuados en IRA es ocho veces mayor en los médicos de la primera mitad de un programa de especialización en atención primaria comparado con los médicos de la segunda mitad del programa OR: 8.74 (95%IC, 4.94-15.46, $p<0.001$), y para practicas inadecuadas es de cinco veces mayor, OR: 5.99 (95%IC, 2.66-13.50, $p<0.001$); la ubicación geográfica y el género femenino fueron factores intrínsecos que se asociaron a menores niveles de CAP. Luego de una intervención multifacética, implementación de una guía de práctica clínica (GPC) en los médicos de un servicio de atención ambulatoria, la prescripción antibiótica se redujo en un 24.5% (42.9% vs. 18.4%, $p<0.0001$) y la prescripción apropiada de antibióticos incrementó en un 44.2% (22.4% vs. 66.6%, $p<0.0001$); los efectos de la intervención permanecieron sin cambios significativos luego de seis años post implementación.

Conclusiones: Las IRAs representan una importante carga de morbilidad ambulatoria en el primer nivel de atención en salud del Ecuador. El uso inapropiado de antibióticos en estas patologías incrementa significativamente el gasto sanitario. Las intervenciones multifacéticas que incluyen estrategias de educación en los prescriptores son herramientas muy efectivas en cambiar el comportamiento y las prácticas de prescripción antibiótica, mejorando el uso eficiente de recursos sanitarios y la calidad de la atención médica.

Palabras clave: antibióticos, infecciones respiratorias, morbilidad, Ecuador

Abstract

Background: The inappropriate prescription of medicines is a public health problem that affects all health care systems. Antibiotics are the most prescribed medicines and upper respiratory tract infections (URTI) are the most treated diseases in primary care. Generally, the treatment of URTI cases does not require the use of antibiotics; however, antibiotics, are frequently prescribed in these diseases. Therefore, it is necessary to explore the problem related to the rational use of antibiotics in URTI in Ecuador; and to determine what factors are related to this public health problem and what are the strategies that could mitigate it.

Aim: To evaluate the current situation of the rational use of antibiotics in upper respiratory tract infections in the first level of health care in Ecuador.

Methods: To achieve the successful development of this research project, a methodology based in three phases was stablished: *1)* A non-experimental, cross-sectional study was conducted to stablish a base line about the use of antibiotics in URTI in the first level of health care in Ecuador, with the purpose of identifying the antibiotic prescription rate and the appropriate and inappropriate prescription rate; on the other hand, a cost of illness study was carried out with the purpose of identifying the use of medical resources and health costs of URTI treatment. *2)* The intrinsic factors that motivate the prescription of antibiotics in primary care physicians were explored through a non-experimental, cross-sectional study that evaluated the knowledges, attitudes, and practices (KAP) related to the prescription of antibiotics in URTI; in addition, the effect of an educational program in primary care in physicians' KAP, was evaluated. *3)* Finally, a quasi-experimental study was conducted that evaluated the short- and late-term effect of a multifaceted intervention in prescribers, through a clinical guideline implementation to reduce the use of antibiotic prescription in URTI.

Results: The antibiotic prescription rate in URTI in the first level of health care in Ecuador was 37.5%, the appropriate and inappropriate antibiotic prescription rate was 9.75% and 90.75%, respectively; junior general practitioners prescribe four times more antibiotics compare to specialist doctors in family medicine, OR: 4.62 (95%CI, 2.00-10.67, $p<0.0001$).

The direct medical cost to the Ministry of Public Health of one episode of URTI in children in 2017 in Ecuador was I$ 37.28; and the total cost in that same year was estimated I$ 50,478 million, follow-up visits and medicine prescriptions represent an important component in URTI costs. The Odds for inadequate knowledge in URTI was eight times higher in physicians in the first half of the primary care postgraduate program compare to the physicians in the second half of the program OR: 8.74 (95%IC, 4.94-15.46, p<0.001); and for inadequate practices of five times higher, OR: 5.99 (95%CI, 2.66-13.50, p<0.001); geographic region and gender, were the intrinsic factors related to lower levels of KAP. After a multifaceted intervention, implementation of a clinical guideline (CG), in physicians of an ambulatory health care center, the antibiotic prescription rate was decreased by 24.5% (42.9% vs. 18.4%, p<0.0001), and the appropriate antibiotic prescription rated was increased by 44.2% (22.4% vs. 66.6%, p<0.0001); the effect of the intervention lasted six years after the implementation without significant changes.

Conclusions: URTI represent an important ambulatory morbidity in the first level of health care in Ecuador. The inappropriate use of antibiotics in these diseases significantly increases health expenditures. Multifaceted interventions in prescribers that include educational strategies are effective tools to change the physician’s behavior and practices in prescribing antibiotics, improving the efficient use of health resources and the quality of medical care.

Keywords: antibiotics, respiratory infection, morbidity, Ecuador

Introducción

El uso racional de los medicamentos se ha convertido en uno de los temas más debatidos a nivel mundial. Según la Organización Mundial de la Salud (OMS) cerca de la mitad de los medicamentos prescritos se dispensan o se venden en forma inapropiada; además, se estima que la mitad de los pacientes toman sus medicamentos de forma incorrecta.

Cuando los medicamentos se utilizan de manera inapropiada se convierten en un problema de salud pública. Una forma inapropiada de consumo de medicamentos resulta en una falla a los tratamientos, un aumento del riesgo de su toxicidad o efectos adversos; y en última instancia, en un incremento de los costos sanitarios, independientemente de que estos provengan de fondos públicos o privados. Esto significa que el uso inapropiado de medicamentos crea impacto en la relación del riesgo/beneficio y costo/beneficio esperado de su uso.

En el primer nivel de atención en salud donde se espera que se resuelvan el 80% de las necesidades en salud de la población se prescriben una gran cantidad de medicamentos. Por tal motivo es deseable que en la atención de primer nivel exista un eficiente uso de los recursos. No obstante, la prescripción inapropiada de medicamentos es altamente frecuente en el primer nivel de atención en salud; y entre ellos, los antibióticos son los medicamentos más prescritos.

Las infecciones del tracto respiratorio superior (IRAs) se ubican dentro de las primeras cinco causas de morbilidad aguda ambulatoria en el primer nivel de atención en salud. Sin embargo, aunque las IRA no requieren un tratamiento antibiótico constituyen la condición en la cual se prescriben una gran cantidad de antibióticos. Se estima que alrededor del 21% de las atenciones ambulatorias pediátricas y del 10% de las atenciones ambulatorias en adultos por IRA, resultan en una prescripción antibiótica.

Las IRAs y sus complicaciones consiguientes imponen una gran carga de enfermedad a los sistemas de salud. Los recursos en salud derivados de su atención incluyen visitas a consultorios, procedimientos diagnósticos, costos de medicamentos de venta libre, costos de medicamentos prescritos, prescripciones de antibióticos, ausencia laboral y escolar; todo esto, puede derivar en un consumo de recursos elevados. Por otro lado, la prescripción innecesaria de antibióticos puede aumentar el desarrollo de resistencia global a los antibióticos aumentando el problema de salud pública.

Esta investigación tiene la intención de evaluar el uso racional de antibióticos en IRAs en el Ecuador. Para lo cual se establece el estudio de la prevalencia de prescripción antibiótica, del costo de la carga de la enfermedad desde la perspectiva de un tercer pagador a fin de determinar su impacto en el sistema nacional de salud pública del Ecuador; y además, se evaluarán los factores relacionados a este problema y las posibles intervenciones a fin de mitigarlo.

Objetivos

General

- Evaluar la situación actual del uso racional de antibióticos en infecciones del tracto respiratorio superior en el primer nivel de atención en salud del Ecuador

Específicos

- Identificar la tasa de prescripción antibiótica en infecciones del tracto respiratorio superior en el primer nivel de atención en salud en el Ecuador.
- Analizar el impacto económico que la atención de las infecciones del tracto respiratorio superior genera en el Sistema Nacional de Salud del Ecuador.
- Identificar factores relacionados a los prescriptores que motivan la prescripción antibiótica en infecciones del tracto respiratorio superior en el primer nivel de atención en salud en el Ecuador.
- Evaluar el efecto que posee una intervención multifacética dirigida a los prescriptores en mejorar el uso racional de antibióticos en infecciones del tracto respiratorio superior en el Ecuador.

Capítulo I. ¿Existe un uso racional de antibióticos en infecciones del tracto respiratorio superior en el primer nivel de atención en salud?

1.1 Uso racional de medicamentos

La prescripción de medicamentos se debe abordar desde la definición del uso racional de medicamentos. La definición de uso racional de medicamentos se formuló en 1985 por la Conferencia de Expertos sobre Uso Racional de los Medicamentos[1], en la cual se indica que "los pacientes reciban fármacos apropiados para sus necesidades clínicas, a dosis ajustadas a su situación particular, durante un periodo adecuado de tiempo y al mínimo costo posible para ellos y para la comunidad". Esta definición incluye el concepto de calidad, de observancia del tratamiento y de eficiencia de los recursos; fue incluido en la estrategia de medicamentos de la Asamblea de la Salud en su resolución WHA39.27[2]. La definición ha sido revisada e integrada en la estrategia farmacéutica de la Organización Mundial de la Salud (OMS), sus objetivos son formular y aplicar medidas de política, asegurar el acceso, asegurar la calidad, la inocuidad y la eficacia, y promover la utilización racional de los medicamentos[3].

El uso racional de los medicamentos se ha convertido en uno de los temas más debatidos. Según la OMS el 50% de los medicamentos que se recetan, se dispensan o se venden en forma inadecuada. Por otro lado, cerca de un tercio de la población mundial carece de acceso a medicamentos esenciales y el 50% de los pacientes los toman de forma incorrecta[4]. Cuando los medicamentos se utilizan de manera inapropiada se convierten en una amenaza para la salud individual y colectiva, derivado de su falta de efecto, toxicidad o efectos no previstos y que van más allá de una relación del riesgo/beneficio adecuado. El uso inapropiado de medicamentos aumenta el riesgo de hospitalización en un 4.1% en individuos jóvenes y hasta en un 16.6% en adultos mayores, siendo estas hospitalizaciones prevenibles en un 24% y en un 88%, respectivamente[5]. Para la obtención de los beneficios que pudiese conllevar la aplicación de un medicamento, se debe precaver su uso apropiado, partiendo desde una correcta prescripción, una apropiada dispensación y su oportuna administración.

Los antibióticos son los medicamentos más prescritos en atención primaria. La tasa anual de uso de antibióticos por cada 100 visitas a establecimientos de salud ambulatorios en los

Estados Unidos (EEUU) se ha estimado en un 16%; sin embargo, la tasa anual en centros de primer nivel se ha calculado en un 18.8%; ubicándolos dentro de las primeras cinco clases de medicamentos utilizados en el primer nivel de atención[6]. En adición, en países de bajos y medianos ingresos económicos (LIC/MIC) la proporción de prescripción antibiótica en atención primaria varia ampliamente, entre el 19.6% y 90.8%, con una prevalencia combinada de prescripción antibiótica del 52%[7]. Además, se ha estimado que la tasa de prescripción antibiótica oral ambulatoria, diferenciada por edad y diagnóstico en adultos y niños en los EEUU, es del 12,6%; sin embargo, el 31% de las prescripciones antibióticas son inapropiadas[8]. El uso inapropiado de medicamentos ha alcanzado su máxima expresión en la inapropiada utilización de los antibióticos.

La resistencia a los antimicrobianos es un problema asociado a la prescripción inapropiada de antibióticos. El desarrollo de la resistencia a los antimicrobianos es un fenómeno natural en las bacterias; sin embargo, algunas actividades humanas facilitan su aparición. El uso inapropiado de antibióticos favorece la aparición y la preponderancia de cepas de microrganismos resistentes; además, las prácticas ineficientes para la prevención y el control de las infecciones contribuyen a que aparezcan y se transmitan nuevas resistencias[9]. Las infecciones causadas por bacterias resistentes se asocian a una mayor morbilidad, mortalidad y coste del tratamiento comparadas con las infecciones producidas por bacterias sensibles de la misma especie[10]. La resistencia antimicrobiana tiene un impacto importante en la salud pública, genera mayor morbilidad, mortalidad y repercute en el gasto sanitario.

1.2 Infecciones respiratorias superiores

Las infecciones del tracto respiratorio superior o respiratorias altas (IRAs) son infecciones que pueden involucrar la boca, nariz, oído, garganta, laringe y tráquea. Las IRAs son un grupo de enfermedades autolimitadas, generalmente denominadas resfriados[11]. Representan alrededor del 3.4% de todas las atenciones médicas en los diferentes escenarios de atención en salud, representan el 74.5% de las consultas médicas en el primer nivel de atención y el 11.7% de consultas de emergencia[12,13]. Además, son responsables de un 20-40% de las atenciones ambulatorias y 12-35% de las atenciones intrahospitalarias en el segundo nivel de atención[14]. Las IRAs representan a las enfermedades infecciosas con mayor carga de morbilidad ambulatoria.

En Ecuador las IRAs son la primera causa de morbilidad ambulatoria en el primer nivel de atención. En el año 2016 se registraron alrededor de 2,407,813 de IRAs, y fueron responsables del 24.17% de todas las consultas ambulatorias en el primer nivel de atención en salud[15].

Las IRAs incluyen a la nasofaringitis, faringitis, amigdalitis y otitis. Cada año, los niños padecen alrededor de 6 a 8 episodios de IRAs, y los adultos de 2 a 4 episodios de IRAs[16,17]. La etiología principal de las IRAs es viral, el 50% por rinovirus, entre el 10% al 15% por coronavirus, del 5 al 15% por virus de la influenza, 5% por el virus de la parainfluenza y 5% por virus sincitial respiratorio[18]. Por otro lado, ciertas bacterias comunes de las vías respiratorias como el *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus* y *Streptococcus pyogenes*, pueden provocar IRAs; los estreptococos del grupo A pueden producir faringitis en el 15-30% en niños y entre un 5-15% en adultos[19].

La patogénesis de las IRAs varía de acuerdo con el microrganismo que la produce. Los rinovirus y coronavirus infectan al individuo a través de su ingreso por vía nasal u ocular, por medio de gotitas aéreas, invaden las células epiteliales de la mucosa respiratoria donde pueden replicarse, produciendo un aumento de la permeabilidad de los vasos sanguíneos y estimulación colinérgica, lo que explica los síntomas que presentan los pacientes[18]. La sintomatología de las IRAs es leve, los síntomas comunes de todas las IRAs incluye fiebre de bajo grado, rinorrea, estornudos, congestión nasal, tos, odinofagia, cefalea y malestar general que frecuentemente se resuelven entre 2 a 3 semanas sin tratamiento específico[20]. Las recomendaciones generales para el tratamiento de las IRAs se orienta a aliviar los síntomas con es el uso de analgésicos y antipiréticos[21–23].

1.3 Uso racional de antibióticos en las infecciones del tracto respiratorio superior

El tratamiento de las IRAs generalmente no requiere el uso de antibióticos. Los antibióticos son ineficaces para tratar los síntomas o para reducir el tiempo de duración de la enfermedad [24]. El Centro de Control y Prevención de Enfermedades (CDC por sus siglas en Ingles) de los EEUU y el Colegio Americano de Médicos de los EEUU no recomiendan el uso generalizado de antibióticos en IRAs[25,26]. El Instituto Nacional de Salud y Excelencia Clínica del Reino Unido (NICE por sus siglas en Ingles), recomienda un tratamiento sintomático para los casos de IRAs y la no prescripción inmediata de antibióticos[27,28].

Existen circunstancias específicas en las cuales la prescripción de antibióticos en IRAs está justificada. El NICE justifica una prescripción inmediata de antibióticos en pacientes en los cuales se evidencia un compromiso del estado general importante; en casos de presentación de síntomas que sugieran enfermedad severa como en neumonía, mastoiditis, absceso peritonsilar, celulitis peritonsilar, complicaciones intraorbitarias o intracraneales; en pacientes con comorbilidades cardiacas, pulmonares, renales, hepáticas, o neuromusculares; y en los casos de inmunosupresión o uso crónico de corticosteroides[28] (Tabla 1).

Aunque las IRAs no requieren un tratamiento antibiótico constituyen la condición en la cual se prescriben mayormente antibióticos. Alrededor del 21% de las atenciones ambulatorias pediátricas y del 10% de las atenciones ambulatorias en adultos, resultan en una prescripción antibiótica. La OMS recomienda que la proporción de pacientes que reciben un antibiótico en escenarios ambulatorios debería ser menor al 30%[29]. No obstante, en los diagnósticos relacionados a enfermedades respiratorias superiores se prescriben excesivamente antibióticos, 72% en niños y 41% en adultos[30,31].

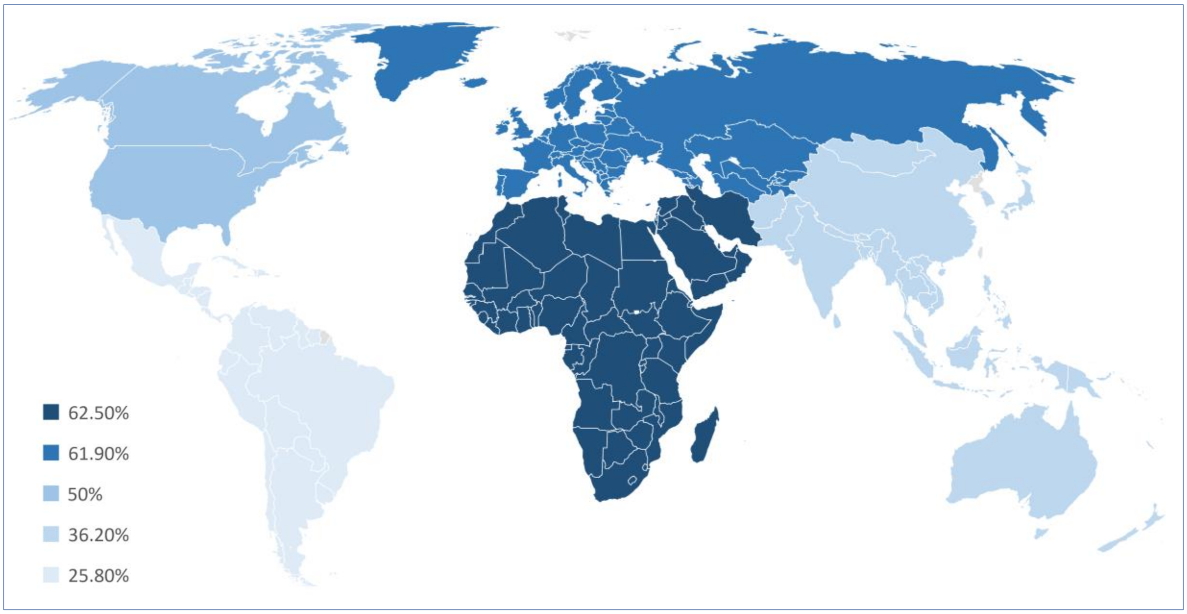
Tabla 1. Criterios para prescripción antibiótica en Infecciones del tracto respiratorio superior

Código CIE-10	Criterios para prescripción antibiótica
H65 Otitis Media No Supurativa **H66** Otitis Media Supurativa y No Especificada	**H65** debe cumplir dos condiciones: Otitis media aguda bilateral **Y** edad <2 años **H65** o **H66:** con presencia de otorrea
J01 Sinusitis Aguda	Debe cumplir todas las condiciones: Fiebre >38C°, Descarga purulenta y dolor facial
J02 Faringitis Aguda **J03** Tonsilitis Aguda	Debe cumplir **3 de los siguientes criterios CENTOR**: − Exudado amigdalino − Linfadenitis o linfoadenopatía cervical anterior dolorosa − Fiebre >38°C − Ausencia de tos
J00 Nasofaringitis Aguda **J01** Sinusitis Aguda **J02** Faringitis Aguda **J03** Tonsilitis Aguda **J04** Laringitis Aguda y Traqueítis **J05** Croup y Epiglotitis **J10** Influenza	**Debe cumplir los siguientes criterios**: − Presencia de una o más comorbilidades: Cardiaca, Pulmonar, Renal, Hepática, Neuromuscular, Inmunosupresión, Fibrosis quística, Diabetes Mellitus. **O** Edad <2 años **con** historia de prematuridad **O** − Edad >65 años **Y** presencia de tos **Y dos o más** de los siguiente: ▪ Hospitalización reciente ▪ Diabetes mellitus ▪ Historia falla cardíaca ▪ Uso actual de corticosteroides **O** − Edad >80 años **Y** presencia de tos **Y uno o más** de los siguientes: ▪ Hospitalización reciente ▪ Diabetes mellitus ▪ Historia falla cardíaca ▪ Uso actual de corticosteroides

Elaborado por autor

El uso de antibióticos en IRAs es general a nivel mundial. En países con ingresos económicos altos, como EEUU y Canadá, se estima que alrededor del 50% de las prescripciones antibióticas se enfocan en el tratamiento de rinosinusitis, otitis media aguda supurativa y faringoamigdalitis aguda[32–36]. En Europa la situación de prescripción antibiótica en IRAs en escenarios de atención primaria es similar, con un estimado de tasa de prescripción de 26,7% en España, 74,9% en Italia, 74,6% en Hungría, 37% en Noruega, 71,4% en Polonia, 79.2 en Alemania, 31% en Bélgica, 38% en Suecia y 56.6% en Reino Unido[37]. En adición, en niños de países en vías de desarrollo o en transición, son prescritos antibióticos inapropiadamente en IRAs, esta situación ha ido incrementando en el tiempo, de un 42% antes de 1990 hasta un 72% entre el 2006 y 2009[38]. (Figura 1).

Figura 1. Proporción de prescripción antibiótica inapropiada en IRAs a nivel internacional



Elaborado por autor.

1.4 Consideraciones económicas

Las IRAs y sus complicaciones imponen una gran carga de enfermedad en los sistemas de salud. Los recursos en salud consumidos durante un episodio de IRAs son las visitas a consultorios, los costos de medicamentos de venta libre, los costos de medicamentos prescritos, las prescripciones de antibióticos que pueden derivar en el desarrollo de resistencia global a los antibióticos, y la ausencia laboral y escolar. Se ha estimado en EEUU que los resfriados puede generar un costo de alrededor de $ 40 mil millones de dólares por año[39], contando con un costo directo de $ 17 mil millones de dólares por año, de los cuales $ 7,7 mil millones son generados en atenciones médicas, $ 2,9 mil millones en medicación de venta libre, $ 1,1 mil millones en uso de antibióticos y $ 400 millones en medicación para alivio de los síntomas. Por otro lado, se estimó que el resfriado común genera alrededor de $ 22,5 mil millones de costos indirectos por año, relacionados al ausentismo laboral y escolar.

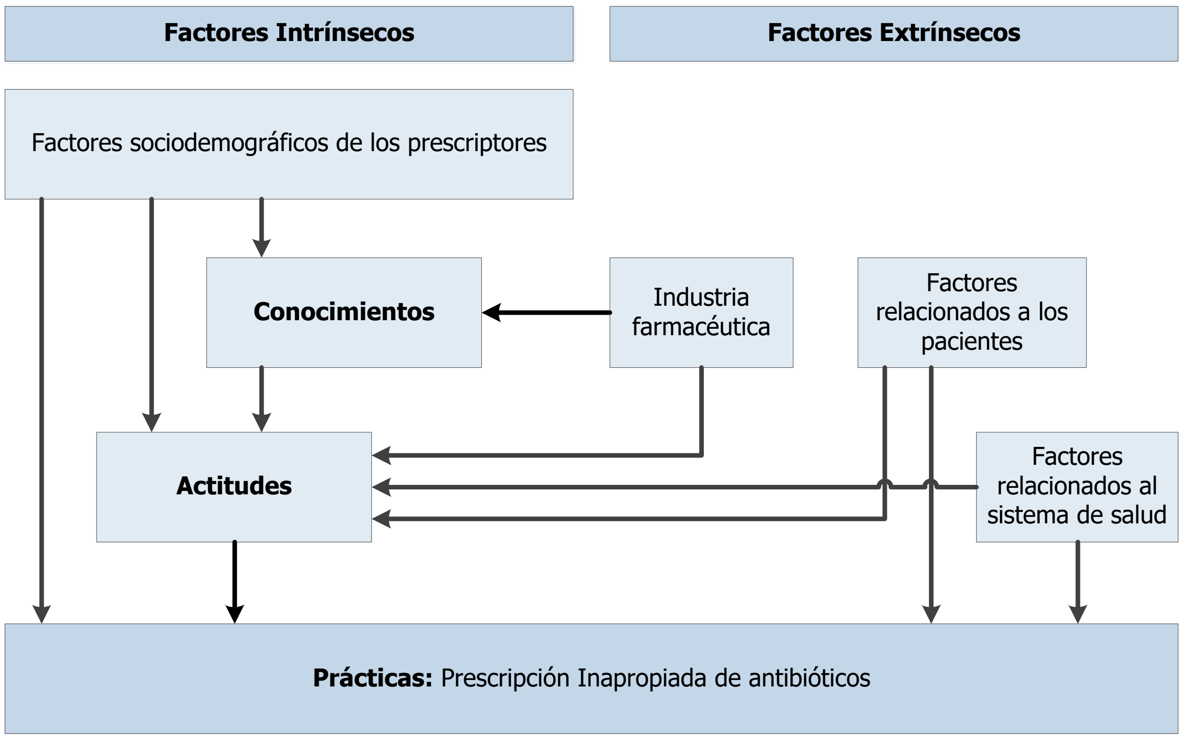
La prescripción antibiótica en IRAs representa un gasto farmacéutico importante. En 2007, los estadounidenses gastaron $ 3.6 mil millones de dólares en medicamentos de venta libre y en el Reino Unido se gastaron £ 100 millones en alivio sintomático del resfriado común en 2005[40]. En Japón en 2016, se estimó que le coste del uso inapropiado de antibióticos en IRAs desde la perspectiva de del tercer pagador (sistema de salud) representa entre 300 a 400 millones de dólares anualmente[41]. En Grecia entre 2010 y 2013 se estimó que el gasto en antibióticos en escenarios ambulatorios del tratamiento de IRAs es de 31,9 millones de euros en pacientes pediátricos y de alrededor de 43 millones de euros en adultos[42,43]. El uso inapropiado de antibióticos en IRAs produce un gasto farmacéutico innecesario, el cual puede ser incurrido por el paciente y/o el sistema de salud. La determinación del consumo de recursos y costos asociados en la atención de estas enfermedades puede permitir identificar áreas en donde se podrían instaurar estrategias de contención de costos.

1.5 Factores relacionados a la prescripción antibiótica en las infecciones del tracto respiratorio superior

El uso inapropiado de medicamentos, incluido los antibióticos, está influenciado por múltiples factores. La multi-morbilidad, el género de los pacientes y las experiencias personales de los médicos en su práctica diaria han sido reportados como factores que influyen en la prescripción[44]. Por otro lado, características sociodemográficas de los prescriptores, el conocimiento de la evidencia médica, recomendaciones actualizados y la aceptación o credibilidad del personal de salud de éstas, influyen en la prescripción de medicamentos[45,46]. Otros factores como las características organizacionales de los sistemas de salud, por ejemplo la disposición de tiempo en consulta, programas preventivos y educativos en enfermedades, disponibilidad de alternativas terapéuticas, presión de la industria farmacéutica y el respaldo institucional a los profesionales de la salud, también influyen en la prescripción de medicamentos[47]. Los factores relacionados a la calidad de la prescripción pueden provenir tanto de características de los pacientes, prescriptores y de las características organizacionales de los sistemas de salud.

Existe existe una distinción bien establecida entre factores intrínsecos y factores extrínsecos que influyen la prescripción antibiótica. Estos factores no son totalmente independientes, sino que se encuentran interrelacionados y una comprensión profunda de estos factores es fundamental para explicar la prescripción antibiótica. Texeira et al.[48] propone un marco conceptual que sistematiza esta interconexión de factores que influyen en los conocimientos y actitudes de los prescriptores, y que finalmente derivan a una práctica de prescripción antibiótica (Figura. 2).

Figura 2. Marco teórico de la influencia y la interconexión entre los factores que influyen en la prescripción de antibióticos



Adaptado de Texeira et al.

La influencia adecuada de todos los factores en un marco de conocimientos, actitudes y prácticas de adecuada prescripción antibiótica permitirá un uso racional de los mismos. La prescripción racional se consigue cuando el profesional bien informado, haciendo uso de su mejor criterio, prescribe al paciente un medicamento bien seleccionado, en la dosis adecuada durante el periodo de tiempo apropiado y al menor coste posible[49]. Explorar los factores que influyen en el uso racional de antibióticos en IRAs en el primer nivel de atención en salud podría maximizar la efectividad, minimizar los riesgos y costes del tratamiento, teniendo además consideración de las preferencias de los pacientes.

1.6 Estrategias para mejorar el uso racional de antibióticos en las infecciones del tracto respiratorio superior

Existen varias estrategias que se han desarrollado con el objetivo de promover el uso racional de medicamentos, entre ellos los antibióticos. Las estrategias para mejorar el uso de medicamentos pueden ser divididas en intervenciones educacionales, gerenciales, financieras y regulatorias. LeGrand et al.[50] realizó un estudio de las intervenciones para el uso racional de medicamentos, identificando intervenciones dirigidas a los prescriptores e intervenciones dirigidas a los consumidores o pacientes pero no estimó el efecto de las mismas, las limitaciones identificadas fueron la escaza cantidad de información para evaluar estrategias para mejorar la prescripción de medicamentos, el contexto en el que se realizan las investigaciones y la pobre calidad metodológica de los estudios. El efecto de las intervenciones destinadas a mejorar la prescripción de medicamentos no es claro y su impacto durante el tiempo tampoco ha sido evaluado.

Las intervenciones para mejorar el uso racional de antibióticos pueden tener un carácter persuasivo, restrictivo o estructural. Estas intervenciones pueden abarcar varias estrategias desde el punto de vista del prescriptor, del paciente o del sistema organizacional[51]. Las estrategias educacionales se basan principalmente en el estudio de los patrones de prescripción y las medidas que pueden cambiar la conducta del prescriptor y la expectativa del paciente. Las estrategias gerenciales tienen como objetivo mejorar la práctica clínica para optimizar el uso de medicamentos, mejorando el proceso estructural de decisión. Las medidas restrictivas, como limitar la prescripción de medicamentos por tipo de diagnóstico, uso especializado de un grupo de medicamentos, justificación del uso de medicamentos y restricciones por niveles de atención son estrategias de tipo regulatorio. Las estrategias de tipo financiero tienen como objetivo crear fondos específicos para el uso de algunos medicamentos o; por otro lado, la creación de impuestos por uso de medicamentos especiales. No obstante, las intervenciones que incluyen material educativo para médicos, pacientes y o cuidadores, son las más efectivas para reducir el uso de antibióticos en los casos de IRAs, pero dependen del contexto en donde se aplican[51,52]. Evaluar el efecto de una intervención multifacética es importante en el contexto de la atención de primer nivel en el Ecuador; de esta forma, se puede establecer estrategias efectivas a fin de mejorar el uso racional de antibióticos.

Capítulo II. Metodología

Se trata de una investigación que evalúa el uso racional de antibióticos en IRAs en el primer nivel de atención en salud en el Ecuador. Para alcanzar el desarrollo adecuado de la investigación en planteó una metodología en tres fases ligadas al cumplimiento de los objetivos específicos a través de diferentes estudios de investigación:

1. En la primera fase se estableció la metodología para identificar una línea de base del problema del uso de antibióticos en IRAs en el primer nivel de atención en Ecuador. Identificando la tasa de prescripción antibiótica y el consumo de recursos en salud en la atención de dichas enfermedades, tomando como escenario un Distrito de Salud de la ciudad de Quito en Ecuador.
2. La segunda etapa de investigación permitió identificar factores que motivan la prescripción antibiótica a través de la descripción de las cualidades del fenómeno de prescripción antibiótica en una muestra de prescriptores del primer nivel de atención en salud, en cinco provincias del Ecuador. Esto permitió identificar posibles factores no clínicos o no dependientes del paciente que influyen en la decisión del prescriptor.
3. La tercera fase permitió concluir la investigación con la identificación y evaluación del efecto de una intervención destinadas a mejorar la prescripción antibiótica en los prescriptores, a través de una intervención multifacética dirigida a los médicos.

2.1 Sitio de estudio y población

La investigación se llevó a cabo en Ecuador, y tiene un carácter nacional. Ecuador se encuentra ubicado en América del Sur, posee cuatro regiones geográficas bien diferenciadas, Costa, Sierra, Amazonia y Región Insular, posee una superficie total de 256.370 Km^2, y la estimación poblacional para el año 2019 fue de 17 millones de habitantes.

El Sistema Nacional de Salud del Ecuador (SNS), está dividido en un sistema público y uno privado. El sistema público se encuentra subdividido en el Ministerio de Salud Pública (MSP), el Instituto Ecuatoriano de Seguridad Social (IESS), el Instituto de Seguridad Social de las Fuerzas Armadas (ISSFA), el Instituto de Seguridad Social de la Policía (ISSPOL), y el Seguro Social Campesino (como dependencia del IESS). El subsistema de salud público tiene una red integrada de salud para la atención de la población, que también se conecta con el subsistema privado en instituciones de convenio.

Para el presente trabajo de investigación se incluyó fuentes primarias y secundarias de datos. Los datos recolectados pueden ser extrapolados para todo el país.

2.2 Diseño de estudio

Se estableció una línea de base en relación con la tasa de prescripción antibiótica en IRAs en el primer nivel de atención en salud a través de un estudio observacional y analítico en los Centros Ambulatorios de Salud del MSP en el Distrito 17D03 durante el año 2015. Se determinó además la tasa de prescripción adecuada e inadecuada de antibióticos.

Para determinar las implicaciones económicas para el SNS de Ecuador, se realizó un estudio de costo de enfermedad bajo la perspectiva del tercer pagador, en este caso el MSP. La perspectiva del estudio incluyó todos los recursos utilizados para el diagnóstico y tratamiento de los pacientes con infecciones del tracto respiratorio superior desde su primera consulta médica hasta su seguimiento de cuatro semanas. El estudio se realizó en los Centros Ambulatorios de Salud del MSP en el Distrito 17D03 durante el año 2017. Se utilizó un abordaje de micro-costeo a través de la revisión de las historias clínicas de los pacientes.

Para identificar los factores relacionados a la prescripción antibiótica en IRAs en los prescriptores se realizó un estudio observacional analítico, a través de una encuesta on-line de conocimientos, actitudes y prácticas (CAP) en los profesionales de salud. El estudio se llevó a cabo en cinco provincias del país, Esmeraldas, Imbabura, Manabí, Pichincha, y Santo Domingo de los Tsáchilas. Se realizó un análisis entre las diferentes variables sociales y los CAP de los médicos. Se evaluó además la relación de un programa educativo de especialización en medicina familiar de atención de primer nivel y los CAP de los médicos.

La evaluación de estrategias para disminuir la prescripción antibiótica y mejorar la prescripción adecuada de antibióticos en IRAs se realizó a través de un estudio cuasi-experimental, de medición de efectos antes y después de la intervención. La intervención constó de la implementación de una GPC en un escenario controlado en un servicio de emergencia de un hospital. Se realizó un análisis de la prescripción antibiótica en IRAs pre-implementación y post-implementación, a corto y a largo plazo. El proceso de implementación incluyó la concientización del personal de salud, difusión de material educativo, una campaña educacional, retroalimentación activa y constante, y un proceso de sostenibilidad de la intervención a largo plazo, lo que denota su carácter de multifacética.

2.3 Fuentes de información

El estudio utilizó las siguientes fuentes de información:

1. Historias clínicas de pacientes atendidos por infecciones del tracto respiratorio superior en los Centros de Atención de Primer nivel del Distrito 17D03 del Ministerio de Salud Pública del Ecuador durante el año 2015 y 2017.
2. Tarifario Nacional de Prestación de Servicios para la red pública y privada del Sistema Nacional de Salud del Ecuador.
3. Documentos oficiales de compra de insumos y medicamentos de farmacia los Centros de Atención de Primer nivel del Distrito 17D03 del Ministerio de Salud Pública del Ecuador.
4. Base de datos de compras públicas del Servicio Nacional de Contratación Pública (SERCOP) del Ecuador.
5. Historias clínicas de pacientes atendidos por infecciones del tracto respiratorio superior en el servicio de emergencia de un hospital privado de la ciudad de Quito-Ecuador en los periodos de medición de la intervención.

2.4 Análisis de datos

Con el fin de establecer la tasa de prescripción antibiótica en IRAs en el primer nivel de atención en salud en Ecuador, se consideró la tasa de prescripción antibiótica como el número de prescripciones de antibióticos dividido para el total de los pacientes con un diagnóstico de IRA según la Clasificación Internacional de Enfermedades CIE-10 (Tabla 1) durante el periodo de estudio. La tasa de prescripción antibiótica adecuada se calculó en base al número de pacientes que necesitaban antibiótico según recomendaciones una guía de referencia en relación con el número de pacientes que recibió antibióticos. La determinación de la tasa de prescripción adecuada permitió estimar la prescripción excesiva que ocurrió en el periodo de estudio, tasa de prescripción inadecuada. Se realizó además un modelo de regresión logística que permitiera predecir la prescripción antibiótica en relación con las diferentes características de los prescriptores y pacientes.

Para el estudio de costo de enfermedad de las infecciones respiratorias altas, se midió el consumo de recursos en sus unidades naturales (cantidades) y la valoración de los recursos en unidades monetarias. La unidad de medida de los costos fueron dólares internacionales (I$) a fin de obtener resultados comparables a nivel internacional, utilizando el factor de conversión para el periodo de estudio según la paridad de poder adquisitivo. Se calculó el costo por episodio y se clasificó el consumo de recursos en base a su naturaleza: atenciones, métodos de diagnóstico, procedimientos y medicamentos. Se estimó el costo anual que se incurre en el gasto en para el MSP mediante la fórmula: (Costo por episodio por paciente) x (Total de número de episodios por año 2017).

El análisis de los datos de los factores relacionados a la prescripción antibiótica en IRAs en los prescriptores se los realizó a través de un sistema de calificación en cada dominio de CAP (scores). Cada uno de los scores se analizó como una variable continua que se calculó mediante la suma simple de la cantidad de respuestas correctas para cada dominio CAP, posteriormente la variable fue convertida en una variable categórica en base a un puntaje de 60% de respuestas acertadas en cada dominio, cada score fue considerado como una variable dependiente. Las variables independientes fueron elegidas en relación con al marco conceptual de factores intrínsecos de los prescriptores (Figura 2). Finalmente se realizó un análisis bivariado entre las variables a través de un modelo de regresión logística.

La determinación de la eficacia de la intervención de la GPC se la realizó mediante la determinación de la tasa de prescripción antibiótica pre-implementación y post-implementación a corto y largo plazo. Las diferencias entre las proporciones de prescripción antibiótica fueron evaluadas a través de una prueba z (Prueba t para proporciones independientes). Además, se realizó un subanálisis por diagnósticos y grupos etarios.

2.5 Consideraciones bioéticas

Los diferentes estudios realizados a fin de completar los objetivos específicos del proyecto de investigación contaron con la aprobación de un Comité de Ética de la Investigación en Seres Humanos (CEISH) autorizado en el Ecuador.

El manejo de los datos cumplió con un estricto protocolo de anonimizar los datos, mantener la confidencialidad y resguardar de la información. Para la valoración de los factores de prescripción en los médicos se llevó a cabo un procedimiento de consentimiento informado.

Capítulo III. Resultados

3.1 Artículos publicados

- Sánchez Choez, X., Armijos Acurio, M. L., & Jimbo Sotomayor, R. E. (2018). “Appropriateness and adequacy of antibiotic prescription for upper respiratory tract infections in ambulatory health care centers in Ecuador.” *BMC Pharmacology and Toxicology*, *19*(1), 46. https://doi.org/10.1186/s40360-018-0237-y

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Sánchez Choez *et al. BMC Pharmacology and Toxicology* (2018) 19:46
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BMC Pharmacology and Toxicology

RESEARCH ARTICLE Open Access

"Appropriateness and adequacy of antibiotic prescription for upper respiratory tract infections in ambulatory health care centers in Ecuador"

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Abstract

Background: Upper respiratory tract infections are the leading cause of misuse of antibiotics, a problem that leads to unnecessary adverse events and antibiotic resistance. Antibiotic prescription in Ecuador was analyzed in order to evaluate the state of antibiotic prescribing for upper respiratory tract infections. Both the appropriateness and adequacy of prescribing was evaluated. Appropriateness represents the percentage of prescriptions that are indicated; adequacy refers to the percentage of patients requiring antibiotics who are treated.

Methods: The aim of the study is to analyze the appropriateness and adequacy of antibiotic prescription for upper respiratory tract infections in the Ambulatory Health Centers of the Ministry of Public Health of Ecuador. This is a cross-sectional study of patients from one Health Center of the Ministry of Public Health in the District 17D03 in Ecuador during 2015 with upper respiratory tract infection as a primary diagnosis.

Results: We included a total of 1393 patients in the analysis. Out of the 1393 patients identified, 523 were prescribed antibiotics, constituting an antibiotic prescription rate of 37.5%, and 51 required antibiotics, reflecting a real need of antibiotics of 3.7%. Appropriateness: Of these 523 patients who were treated, 51 required an antibiotic, resulting in an appropriate antibiotic prescription rate of 9.75%. Adequacy: When analyzing each individual case, 33 of these 51 patients received an antibiotic, constituting an adequate prescription rate of 64.7%.

Conclusions: The results of our study report a 90.25% of inappropriate prescription. The antibiotic prescription, appropriate prescription, and adequate prescription rates show the need for implementation of strategies in order to reduce them. Related aspects regarding prescriber's behavior and the patient's expectations should be analyzed.

Keywords: Antibiotic, Prescription, Family practice, Health systems and services, Anti-bacterial agents, Drug utilization, Practice guidelines

Background

Appropriate and adequate use of drugs is now one of the most commonly debated topics in public health. According to the WHO, only 50% of all prescribed medications are dispensed or sold in an appropriate way [1]. On the other hand, about one third of the world population lacks access to drugs considered as essential drugs by the WHO [2]. According to the WHO, the rational use of drugs requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" [3]. The appropriate prescription rate is the number of cases that need treatment divided by the number of cases that receive it. It has the objective of maximizing the effectiveness of a treatment, minimizing the risk and costs, and taking into consideration the preference of the patients [4]. Adequate prescription rate is the number of cases that needs and receives

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treatment divided by the number of cases that need it. Adequate prescription allows us to analyze if patients that require treatment are receiving it.

Differences in prescription can be due to both the prescriber and the patient. Studies have shown that factors like gender, multi-morbidity and previous personal experiences can influence prescription [5, 6]. Prescription is also influenced by the health provider's knowledge of evidence based medicine, current guidelines, personal experience and lack of time or availability of drugs [7].

A 2016 study by Fleming-Dutra et al. in the United States shows a rate of inappropriate oral antibiotic prescription of about 50% in upper respiratory tract infection (URTI), adjusted by age and diagnostic in adults and children [8]. Another study in children in France finds results that suggest a 76% rate of inappropriate prescription of antibiotics for any pediatric diagnosis in primary health care and that URTI are the leading cause of misuse of antibiotics. [9].

A prospective study with 3402 patients with acute cough from 13 European countries analyzed the variation in prescription of antibiotics in primary care. Their results showed a high prescription rate, in all countries included that ranged between 20 and 90% (media of 53%) [10]. Another study from four Latin American countries found that 33% of patients with a suspicion of URTI in primary care centers that were included in the study were prescribed antibiotics [11].

Even though resistance to antibiotics is a natural phenomenon in bacteria, human activities have potentiated its expansion, favoring the appearance of resistant strains. The lack of efficient practices for prevention and control of infections has also contributed to the emergence of new resistances [12]. The inappropriate use of antimicrobials increases the risk of drug-resistant microorganisms [13].

Costelloe, et al. in 2010, demonstrate a strong association between the prescription of antibiotics in primary care and antimicrobial resistance in URTI [14]. It has been reported that antibiotic resistance to microorganisms such as *Staphylococcus aureus*, enterococci, and gram-negative bacilli, are associated with an increase in mortality, morbidity, days of hospitalization and health costs [15]. The increase in health costs associated to antibiotic resistance is due to the longer duration of disease and the need for additional diagnostic tests and high-cost antibiotics. [16].

Due to the large impact on health, antibiotic prescription in Ecuador was analyzed in order to evaluate if the tendency aligns with the misuse of antibiotics occurring around the world. Defining the scope of the problem will allow for further analysis and policy implementation in the country.

Methods

The aim of this study was to analyze the appropriateness and adequacy of antibiotic prescription for URTI in the Ambulatory Health Centers of the Ministry of Public Health of Ecuador in the District 17D03 during 2015. The design of this cross-sectional study of the appropriateness and adequacy of antibiotic prescription imitates similar studies from different settings [8, 17–19] allowing us to obtain comparable results. We considered "Appropriate prescription rate" as the number of appropriate antibiotic prescriptions divided by all patients receiving antibiotics. Our definition of "Adequate prescription rate" is the number of patients that need and receive antibiotics divided by the number of patients that need it. The purpose of measuring the appropriate prescription rate is to identify the over-prescription that could be occurring. On the other hand, the purpose of analyzing the "Adequate prescription rate" is to identify cases of patients that needed antibiotics and did not receive treatment.

Data source

The data source for the variables included in this study are the Electronic Health Records (EHR) of all the patients from one Health Center of the Ministry of Public Health in the District 17D03 in Ecuador during 2015 with URTI as a primary diagnosis. This district has been using EHR since 2010. Prescribers enter the information directly into the EHR on a computer during the outpatient appointment. Information was manually extracted from the EHR simultaneously by two peer reviewers, according to the following criteria:

Inclusion criteria: Patients 3 months of age and above who required clinical care for URTI in the Ambulatory Health Centers of the Ministry of Public Health in the District 17D03 in 2015.

Exclusion criteria: 1) Patients who received clinical care in the ambulatory health centers of the Ministry of Public Health that are not a part of the D1703 district; 2) Patients who received clinical care in ambulatory health centers that are not a part of the Ministry of Public Health in the D1703 district.

The International Classification of Disease (ICD) – 10 was used for selection of the diagnosis criteria for URTI, where we considered codes J00-J06, J10, J11, H65, H66 (Table 1). After individual data extraction, information was compared, and reached a consensus of inclusion or exclusion for each patient. An additional text file of description of variables shows the variables collected for the analysis of appropriateness and adequacy of antibiotic prescription (see Additional file 1).

The patients included in this study were those attended by the 5 types of health professionals that work in the designated health center and that diagnosed

Table 1 ICD-10 Codes considered as "upper respiratory tract infections" for the purpose of this study

We considered an upper respiratory tract infection diagnosis as any diagnosis registered according to the ICD-10 classification, as any the following:

- JOO Acute nasopharyngitis [common cold]
- JO1 Acute sinusitis (includes J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, J01.9)
- JO2 Acute pharyngitis (includes J02.0, J02.8, J02.9)
- JO3 Acute tonsillitis (includes J03.0, J03.8, J03.9)
- JO4 Acute laryngitis and tracheitis (includes J04.0, J04.1, J04.2)
- JO5 Acute obstructive laryngitis [croup] and epiglottitis
- JO6 Acute upper respiratory infections of multiple and unspecified sites (includes J06.0, J06.8, J06.9)
- J10 Influenza due to other identified influenza virus (includes J10.1)
- J11 Influenza due to unidentified influenza virus (includes J11.1)

We will consider as part of the upper respiratory tract infections, diseases of the middle ear categorized according to ICD-10 as:

- H65 Nonsuppurative otitis media
- H66 Suppurative and nonspecified otitis media

patients with URTI. These health professionals are classified as:

- Rural Medical Trainees: Medical Doctor that has recently completed their degree and is performing a year of community service as a health professional in a rural location as a prerequisite for medical practice in Ecuador.
- General Practitioner: Medical Doctor that has completed the year of community service as a health professional and can practice medicine freely in Ecuador.
- Family Medicine Doctor: Medical Doctor that has performed a postgraduate degree of 3 years in General Practice and is considered a specialist in Ecuador.
- Psychiatrists: Medical Doctor that has performed a postgraduate degree of 3 years in Psychiatry and is considered a specialist in Ecuador.
- Pediatricians: Medical Doctor that has performed a postgraduate degree of 3–4 years in Pediatrics and is considered a specialist in Ecuador.

Sample

The sample was defined as all the patients that met the inclusion criteria and that had complete information in their EHR. Our sample is of 1393 patients.

Assessment of appropriateness and adequacy of antibiotic prescription

For this study, "Appropriate antibiotic prescription" is considered according to the standards defined in the Clinical Guideline for "Respiratory Tract Infections (self-limiting): prescribing antibiotics CG69" by the National Institute for Health and Care Excellence (NICE), considering the lack of a National clinical guideline for URTI in Ecuador. Table 2 describes the criteria for cases that needed antibiotic prescription according to each ICD category, as described in the NICE Clinical Guideline. Need for antibiotics was assessed by two reviewers separately in order to identify the cases that met the

Table 2 Guide for Classifying Appropriate Antibiotic Prescription: using ICD-10 codes to classify appropriate diagnosis of disease according to the symptoms and signs presented in the patients in the sample

ICD-10 code	Criteria for Appropriate Antibiotic Prescription
H65 Nonsuppurative otitis media H66 Suppurative and nonspecified otitis media	H65 must meet both conditions: presence of Acute Bilateral Otitis media AND age < 2 H65 or H66 with presence of otorrhea
J01 Acute sinusitis	Must meet all conditions: Fever of >38C°, purulent discharge and facial pain
JO2 Acute pharyngitis JO3 Acute tonsillitis	Must meet 3 of the following CENTOR criteria: Presence of tonsilar exudate Presence of painful anterior cervical lymphadenopathy or lymphadenitis Fever (> 38°) Absence of cough
JOO Acute nasopharyngitis [common cold] JO1 Acute sinusitis JO2 Acute pharyngitis JO3 Acute tonsillitis JO4 Acute laryngitis and tracheitis JO5 Acute obstructive laryngitis [croup] and epiglottitis JO6 Acute upper respiratory infections of multiple and unspecified sites J10 Influenza due to other identified influenza virus J11 Influenza due to unidentified influenza virus	Must meet any of the following criteria: Presence of one or more of the following comorbidities: Cardiac, Pulmonary, Renal, Hepatic, Neuromuscular, Immunosuppression, Cystic Fibrosis, Diabetes Mellitus. - OR Age < 2 years old AND history of prematurity OR Age > 65 years old AND presence of cough AND two or more of the following: ▪ Hospitalized in 2014 ▪ Diabetes mellitus ▪ History of cardiac arrest ▪ Current use of corticosteroids OR Age > 80 years old AND presence of cough AND one or more of the following: ▪ Hospitalized in 2014 ▪ Diabetes mellitus ▪ History of cardiac arrest ▪ Current use of corticosteroids

There are no ICD-10 codes for J07 and J08. J09 excluded because it refers to influenza and pneumonia criteria for antibiotic prescription. When a data inconsistency was found in the EHR, the agreement was reached by consensus by the reviewers. We assessed appropriateness of the prescription by identifying the cases that needed treatment divided by the number of cases that received it. We assessed adequacy of the prescription by identifying individual patients that required antibiotic treatment according to Table 2 and evaluated if they received it or not.

The antibiotic prescription rate was defined as the number of antibiotic prescriptions divided by all patients diagnosed with URTI.

Statistical analysis

The variables included in this study were qualitative dichotomous and categorical variables and quantitative continuous variables, an additional text file of description of variables shows this in more detail (see Additional file 1). We performed a descriptive analysis with qualitative variables through frequency distributions, proportions and rates; and of quantitative variables through measures of central tendency and dispersion. We then performed statistical tests to determine the association between antibiotic prescription and several variables through a logistic regression. This regression analyzes the relationship between a dependent variable, antibiotic prescription, and independent variables, controlling for potential confounders. The independent variables were chosen by theoretical relationship to the dependent variable and through bivariate logistic regression models, an additional text file of variables considered for the regression models shows this in more detail (see Additional file 2). In the model we only included variables with a p value of < 0.25. These variables were: gender of prescriber, hours dedicated to clinical practice and category of health professionals. We excluded patient age, prescriber age and gender of patient due to their lack of statistical significance.

For the only categorical variable included, category of health professionals, we analyzed each category and decided to exclude Psychiatrists, due to the low number of consults included in the data. Then we reintroduced some variables that according to literature could be potential confounders (prescriber age and patient age) one by one creating an extended model, but did not find anything of significance. In order to choose between the models to be used, we used Akaike's Information Criteria (AIC). The formula for the final model was:

Log(antibiotic prescription) = b0 + b1*i.levelhp_cate + b2*gender_prescriber + b3*hours_clinical

Where *i.levlehp_cate* is health professional categorized by type, *gender_prescriber* is the gender of the prescriber, and *hours_clinical* is the hours dedicated to clinical practice.

We used STATA v14 and Microsoft Excel as statistical software.

Adequacy of dosage and duration of prescription of antibiotics

We analyzed adequate dosage of antibiotics based on several clinical Guidelines defined in Table 3 [20–25]. This analysis consisted in categorizing prescriptions in those that were under the recommended dose, over the recommended dose, and adequate dose. We also analyzed the number of prescriptions that met the recommended amount of days of treatment. We considered 7 to 10 days as the adequate duration of treatment for all antibiotics included, except for Azithromycin and Penicillin benzathine. We considered 5 days as an adequate duration of treatment for Azithromycin and a single dose for Benzathine penicillin. To define the duration of treatment we used the same clinical guidelines used for the definition of adequate dosage. This analysis was done for each prescription in the patients included in this study.

Results

The general characteristics of our sample are described in Table 4.

Adequacy and appropriateness of antibiotic prescription

We included 1393 patients that met our inclusion criteria in the analysis that were attended by 21 health professionals (4 Rural Trainees, 7 General Practitioners, 6 Family Medicine Doctors, 3 Pediatricians and 1 Psychiatrist). Out of the 1393 patients, 523 were prescribed antibiotics, constituting an antibiotic prescription rate of 37.5%. Of these 523 patients, 51 required an antibiotic, resulting in an appropriate antibiotic prescription rate of 9.75%. The 51 patients in our sample that needed antibiotics represent 3.66% of all patients. When analyzing each individual case, 33 of these 51 patients received an antibiotic, constituting an adequate prescription rate of 64.7%. We then debriefed the data by different diagnosis according to the ICD-10 codes (Table 5). Acute nasopharyngitis (J00), also known as common cold, represents 41.73% of all diagnoses. Only 2.41% of the cases of common cold had other criteria requiring antibiotics and 2.91% of the cases received antibiotics. Nevertheless, of the cases of J00 that needed antibiotics, only 5.88% received them, the rest of antibiotics prescribed were for cases where it was not needed. This scenario is very different when analyzing prescription for J02, J03 or J06. The results for J02 show us that 51.3% of patients with this diagnosis were prescribed antibiotics, when only 2.94% needed them. The case for acute tonsillitis (J03) is that 83.13% of the cases were prescribed antibiotics, when 9.64% needed them. For Acute upper respiratory infections of multiple and unspecified sites (J06) 61.5%

Table 3 Antibiotic Regimens Recommended for URTI

Antibiotic	Dose	Reference
Amoxicillin	*Pediatric:* 50 mg/kg once daily or 25 mg/kg twice daily, High dose 80-90 mg/kg in 2 divided doses (acute otitis media/acute bacterial sinusitis) *Adult:* 500 mg – 2000 mg twice daily	[20, 21]
Cephalexin	*Pediatric:* 20 mg/kg/dose twice daily* *Adult:*500 mg twice daily	[20, 21]
Benzathine Penicillin G	*Pediatric:* < 27 kg: 600000 U; ≥27 kg: 1200000 U single dose *Adult:* 1200000 U single dose	[20, 21]
Clarithromycin	*Pediatric:* 7.5 mg/kg/dose twice daily *Adult:* 500 mg twice daily	[20, 21]
Azithromycin	*Pediatric:* 12 mg/kg once daily *Adult:* 500 mg daily	[20, 21]
Erythromycin	*Pediatric:* 50 mg/Kg divided four times *Adult:* 500 mg	[24, 25]

Table 4 Characteristics of the sample

Prescriber	*N* (%)
Total of prescribers	21 (100%)
Age	
Mean (range)	55 (24–65)
Gender	
Female	14 (66.7%)
Male	7 (33.3%)
Classification of Health Professionals	
Rural Trainees	4 (19%)
General Practitioners	7 (33.3%)
Family medicine Doctors	6 (28.6%)
Pediatricians	3 (14.3%)
Psychiatrist	1 (4.8%)
Patients	*N* (%)
Total of patients	1393 (100%)
Age	
Mean (range)	16 (0–93)
Age Groups	
0–17 years	913 (65.5%)
≥18 years	480 (34.5%)
Gender	
Female	804 (57.7%)
Male	589 (42.3%)
Antibiotic prescription	
0–17 years	
Yes	337 (36.9%)
No	576 (63.1%)
≥18 years	
Yes	186 (38.75%)
No	294 (61.25%)

of cases were prescribed antibiotics, when none of them needed them. In the case of suppurative and nonspecified otitis media (H66), all of them needed antibiotics and were all accurately prescribed.

Our data includes a classification of all health professionals working at the health center that can prescribe antibiotics. These categories are defined as: General Practitioners, Rural Medical Trainees, Family Medicine Doctors, Pediatricians and Psychiatrists. The results for the analysis of antibiotic prescription depending on the classification of health professionals are shown in Table 6.

Our final multiple logistic regression model included antibiotic prescription as a dependent variable and classification of health professional, sex of prescriber and hours of clinical practice of the health professional as independent variables. We found a statistically significant difference in antibiotic prescription by classification of health professional. We used Family Medicine Doctors as the category of reference for the variable of categories of health professionals. When holding gender of prescriber and hours of clinical practice constant, the odds of antibiotic prescription compare to Family Medicine Doctors was of 4.62 times for Rural Medicine Trainees, 2.58 times for Pediatricians and 1.78 times for General Practitioners. When adjusting for classification of health professional and hours of clinical practice, there was no statistically significant difference in prescription between male and female health professionals (Table 7).

Adequacy of dosage and duration of prescription of antibiotics

Without regarding appropriateness or adequacy of prescription, we analyzed adequacy of dosage of all antibiotic prescriptions. The average number of days of treatment prescribed was of 7.26 days (range 1–15 days) with a mode of 7 days. The distribution of antibiotic classes used are shown in Fig. 1.

Table 5 Appropriateness and adequacy of antibiotic prescription according to ICD-10 diagnosis code

ICD-10 Code	# of patients	Prescribed Antibiotic	Cases that needed antibiotic	Cases that needed + received antibiotics	Appropriate prescription rate (%)	Adequate prescription rate (%)
J00	581	17	14	1	82.36	7.14
J01	93	70	4	4	5.71	100
J02	306	157	9	5	3.18	2.94
J03	166	138	16	15	11.59	93.75
J04	34	12	0	0	–	–
J05	8	0	0	0	–	–
J06	191	117	0	0	0	0
J10	0	0	0	0	–	–
J11	0	0	0	0	–	–
H65	8	6	2	2	33.33	100
H66	6	6	6	6	100	100
Total	1393	523	51	33	9.75	64.70

Appropriate and adequate prescription for codes J04, J05, J10, J11 were not estimated. J00 Acute nasopharyngitis [common cold], J01 Acute sinusitis, J02 Acute pharyngitis, J03 Acute tonsillitis, J04 Acute laryngitis and tracheitis, J05 Acute obstructive laryngitis [croup] and epiglottitis, J06 Acute upper respiratory infections of multiple and unspecified sites, J10 Influenza due to other identified influenza virus, J11 Influenza due to unidentified influenza virus

Out of the 523 patients that received antibiotics, 493 (94.3%) were prescribed one antibiotic and 30 (5.7%) were prescribed a combination of antibiotics. The two types of combinations prescribed were 'Benzathine penicillin + Amoxicillin' in 26 patients (86.7%) and 'Benzathine penicillin + Azitromycine' for 4 patients (13.3%). Neither one of the combinations of antibiotics used can be considered as appropriate prescription.

Out of the 337 children that were prescribed antibiotics, 7 received a combination of antibiotics, resulting in 344 antibiotics prescribed in children (single or in combination). Considering weight was reported for all the children included in this study, we were able to calculate the adequate dose for treatment in this group of patients.

Amoxicillin was prescribed in 272 (79.06%) times in children (Fig. 2), of which 6.99% were prescribed with an adequate dose. Out of all the antibiotics prescribed, 16.86% were prescribed with an adequate dose, 48.26% did not reach the adequate dose and 34.88% went over the adequate dose. The description of adequate doses of each antibiotic prescribed for children can be found in Table 8 with further details in Fig. 2.

Out of the 186 adults that were prescribed antibiotics, 23 received a combination of antibiotics, resulting in 209 antibiotics prescribed in adults. Amoxicillin was prescribed 105 times in adults, all of which were prescribed with an adequate dose. Out of all antibiotics prescribed in adults, 93.30% were prescribed with an adequate dose, 0% did not reach the adequate dose and 6.70% went over the adequate dose. The description for the adequate dose of each antibiotic prescribed for adults can be found in Table 8 with further details in Fig. 2.

Table 6 Appropriateness and adequacy of antibiotic prescription according to health professionals

	# of patients	Prescribed Antibiotic	Cases that needed antibiotic	Cases that needed + received antibiotics	Appropriate prescription rate (%)	Adequate prescription rate (%)
General Practitioners ($n = 7$)	692	226	21	14	9.29	66.66
Family Medicine Doctors ($n = 6$)	128	29	9	5	31.03	55.55
Rural Medical Trainees ($n = 4$)	30	17	2	2	11.76	100
Psychiatrists ($n = 1$)	23	23	1	1	4.34	100
Pediatricians ($n = 3$)	520	228	18	11	7.89	61.11
Total	1393	523	51	33	9.75	64.7

Table 7 Odds Ratios of antibiotic prescription

Variable	Odds Ratio (95% CI)	*P*-value
Category of Health Professional		
Family Medicine Doctor (REF)	1.00	
Pediatrician	2.59 (1.64–4.08)	0.000
General Practitioner	1.78 (1.14–2.78)	0.012
Rural Trainee	4.62 (2.00–10.67)	0.000
Gender of Prescriber		
Male (REF)	1.00	
Female	0.89 (0.68–1.18)	0.422
Hours dedicated to clinical practice per day		
0 (REF)	1.00	
1+	1.38 (1.08–1.76)	0.011

REF: Reference category

We then analyzed the number of prescriptions that met the recommended duration of treatment. Out of all the prescriptions, 85.66% met the recommended duration of antibiotic treatment, 9.37% were prescribed less than the recommended duration and 4.97% went over the recommended duration (Table 9).

Discussion

The results of our study report a 90.25% of inappropriate prescription in the Health Center that we evaluated. An estimated average of antibiotic prescription appropriateness from studies around the world, mostly including high – middle income countries, is of about 50% [8, 26–31]. A review of 344 studies between 1990 and 2009 on the treatment of childhood infections in 78 low-middle income countries reported that a high percentage of viral upper respiratory tract infection cases were being treated with antibiotics, with this percentage increasing over time (from 42% before 1990 up to 72% in 2006–2009) [32]. This same study reports 47.1% of inappropriate antibiotic use in URTI in lower-middle income countries and 25.8% for Latin America.

This means that our study reflects almost one eighth of appropriate prescription as compared to other countries around the world. This astonishing number allows us to realize the amount of work that needs to be done locally to improve this rate.

Studies analyzing the same issue also evaluated the rate of antibiotic prescription and compared their results to a baseline. These studies did not consider if those prescriptions were necessary or not or if the dosage of antibiotics was adequate, but they did calculate the rate of antibiotic prescription that we can compare our study to. Cordoba, et al. [11] published a study in 2016 that evaluated antibiotic prescription in patients with a suspected diagnosis of URTI in primary care health centers in four Latin-American countries. The reported antibiotic prescription rate was of 35% in Argentina, 40% in Bolivia, 24% in Paraguay and 27% in Uruguay. Another study by Doubova et al. [33] in Mexico reported more than 61% of children diagnosed with non-streptococcal URTI received antibiotics after the first visit to the health facility. These studies did not evaluate the appropriate prescription rate but show that in a comparable context the rate of antibiotic prescriptions is very similar.

A study about Denmark and Iceland published in 2015 [34] evaluated antibiotic prescription in URTI by general practitioners. The results demonstrate a prescription rate of 59.3% in Denmark and 75.8% in Iceland. Appropriate antibiotic prescription was also assessed by analyzing days of symptoms and Centor Criteria, possibly underestimating

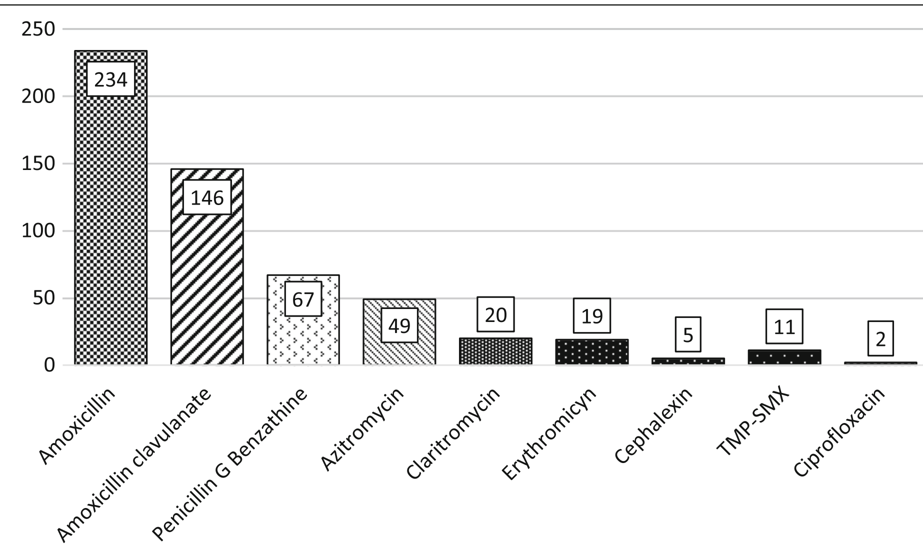

Fig. 1 Distribution of types of antibiotics used. Legend: TMP-SMX: Trimethoprim-sulphamethoxazole

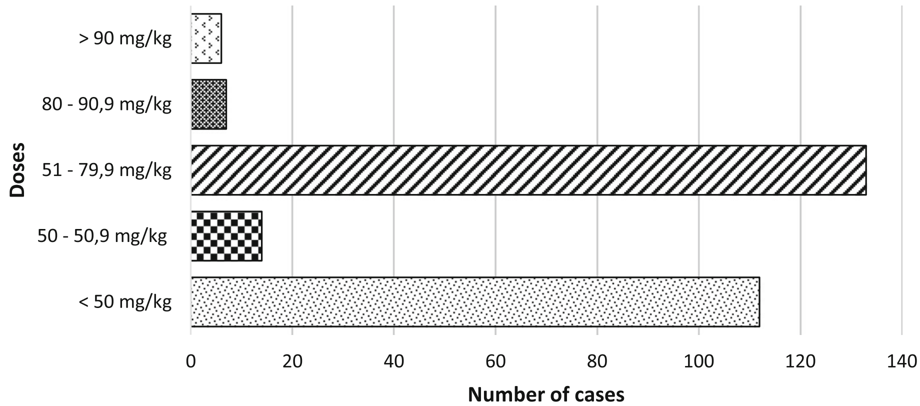

Fig. 2 Amoxicillin used doses in children. Legend: *Doses of 50–50.9 mg/kg/day and 80–90.9 mg/kg/day are considered as adequate according to different diagnosis*

inappropriate use. Their results show a rate of 16.4% for sinusitis and 26.3% for pharyngitis in Denmark and 17.8 and 21.3% in Iceland. Another study done in 6 countries [35] (Switzerland, Denmark, Argentina, Spain, Russia and Lithuania) reported a 50% inappropriate prescription rate and close to 100% inappropriate prescription for rhinopharyngitis and otitis media. These studies show very low appropriate antibiotic prescription rates like the one we found in our study.

It is as important to note the cases of inadequate care, where patients needed antibiotics and did not receive them. Of the total number of cases that required antibiotic prescription, 35.2% did not receive antibiotics. Considering the 93.7% of over-prescription, we would recommend further studies to identify the cause of this rate.

When we analyze the data by diagnosis, we see that the antibiotic prescription rate for common cold is very low, as it should be according to the clinical guideline

Table 8 Appropriateness of antibiotic dose

Antibiotic	Adequate dose	Under adequate dose	Over adequate dose	Total
Pediatric				
Amoxicillin (otitis and sinusitis)	5 (9.09%)	44 (80%)	6 (10.90%)	55
Amoxicillin (other diagnostics)	14 (6.45%)	112 (51.61%)	91 (41.93%)	217
Azithromycin	2 (18.18%)	6 (54.54%)	3 (27.27%)	11
Clarithromycin	6 (30%)	2 (10%)	12 (60%)	20
Erythromycin	15 (83.33%)	2 (11.11%)	1 (5.55%)	18
Penicillin G Benzathine	12 (70.59%)	0 (0%)	5 (29.41%)	17
Cephalexine	2 (50%)	0 (0%)	2 (50%)	4
Trimethoprim-sulphamethoxazole	2 (100%)	0 (0%)	0 (0%)	2
Total	58 (16.86%)	166 (48.26%)	120 (34.88%)	344
Adults				
Amoxicillin (otitis and sinusitis)	20 (100%)	0 (0%)	0 (0%)	20
Amoxicillin (other diagnostics)	85 (100%)	0 (0%)	0 (0%)	85
Azithromycin	37 (97.36%)	0 (0%)	1 (2.63%)	38
Clarithromycin	3 (100%)	0 (0%)	0 (0%)	3
Erythromycin	1 (100%)	0 (0%)	0 (0%)	1
Penicillin G Benzathine	38 (76%)	0 (0%)	12 (24%)	50
Cephalexine	1 (100%)	0 (0%)	0 (0%)	1
Trimethoprim-sulphamethoxazole	9 (100%)	0 (0%)	0 (0%)	9
Ciprofloxacin	1 (50%)	0 (0%)	1 (50%)	2
Total	195 (93.30%)	0 (0%)	14 (6.70%)	209

Table 9 Duration of Prescription of Antibiotics

Antibiotic	Meets recommended duration of treatment	Under recommended duration of treatment	Over recommended duration of treatment	Total
All antibiotics prescribed that have a recommendation of 7–10 days of treatment	388 (88.79%)	24 (5.49%)	25 (5.72%)	437
Azithromycin (Recommendation of 5 days of treatment)	23 (46.94%)	25 (51.02%)	1 (2.04%)	49
Penicillin G Benzathine (Recommendation of one single dose)	37 (100%)	0 (0%)	0 (0%)	37
Total	448 (85.66%)	49 (9.37%)	26 (4.97%)	523

used to describe appropriateness of prescription for this study. This allows us to see that the common cold is not a major problem of antibiotic prescription in this case. The data shows that with any diagnosis different from a common cold, health professionals at this health center tend to prescribe antibiotics at a much higher rate. There is a particular concern with "acute upper respiratory infections of multiple and unspecified sites" (J06), where the group of identified symptoms can reflect other diagnosis, but are classified in this category that leaves an open diagnosis. In this case, patients received antibiotics at a high rate, where it is not appropriate in any case. It seems that the vague definition of this category allows for a lot of variation in treatment prescribed.

In Ecuador, all Medical graduates must do a year of training in a rural area in order to be able to practice as a General Practitioner. In North America and Europe, the General Practitioner is being replaced by Family Medicine Doctors, but in Ecuador the General Practitioner is still the most common type of doctor. In our study, when classifying by health professions, Family Medicine Doctors have the lowest odds of prescribing antibiotics. This could be due to the additional years of training that are required to fulfill that degree, giving them the necessary tools to act. The clinical guideline used in this study does not take into consideration psychiatric comorbidities as a parameter for prescription. Even though psychiatric patients tend to have associated comorbidities that are not considered in this study, patients in primary care health centers usually do not have severe psychiatric disorders that could justify an antibiotic prescription due uniquely to their psychiatric condition.

A study by Del Fiol et al. [36], that analyzes the use of antibiotics in children in two Health Centers in Brazil, reports that 50% of the prescribed dosages of amoxicillin are under the recommended amounts according to Brazilian guidelines. These results are similar to those in our study that show 57.35% of prescriptions were under the recommended dose for the same antibiotic in children.

One of the most relevant limitations in our study is the fact that we relied on retrospective information from EHR. The EHR used in this district allows for registration of all possible variables, but health professionals in many occasions fill in only what is relevant to them about the current reason of consultation, leading to possible incomplete records. Even though during the consultation the health professional may not include the patients' medical history, like history of prematurity, previous hospitalization and some comorbidities, they are able to find this information in the records and can refer to them in order to decide on diagnosis and treatment. This thought process is not contemplated in our analysis, turning it into a limitation for our study and a possible underestimation of appropriate prescription in some cases. Nevertheless, all the variables described in the clinical guidelines were both registered in all patients included and considered for analysis.

Another limitation is the lack of a National Clinical Guideline for upper respiratory tract infections, forcing us to use the NICE guideline. NICE Guidelines consider a global context, instead of only local studies, for their recommendations, which is why we considered this guideline to be appropriate for our study. Ecuador's Minister of Health recommends the use of international guidelines when there is no local guideline provided. NICE guidelines are always taken into consideration when developing national guidelines in Ecuador, which is why we chose this as our reference.

Another limitation to our study is that the sample comes from only one health center. This is due to the lack of an EHR that can report the included variables for each patient, which led to having to extract all the data manually.

Finding a difference both between health professionals in the amount of antibiotics each prescribe can be helpful when targeting individuals for educational plans about antibiotics. If these variables were analyzed in each health center, the specific health professionals that need educational interventions about the appropriate use of antibiotics can be targeted.

Conclusion

In the health center in Ecuador included in the study there is a high rate of inappropriate prescribing of antibiotics; these findings support the need for implementation of strategies to reduce the prescription of antibiotics. Creating this baseline for the whole country instead of one health center could be the first step to realizing the scope of the problem in Ecuador. The antibiotic prescription, appropriate prescription and adequate prescription rates all underscore the need for further research and specific policy analysis and implementation in developing countries. Knowing that inadequate antibiotic prescribing is a problem in this local setting can contribute to an appropriate prescription policy.

Additional files

Additional file 1: "Description of Variables", shows variables collected for the analysis of appropriateness and adequacy of antibiotic prescription. (DOCX 23 kb)

Additional file 2: "Variables considered for the regression model", shows variables chosen for bivariate logistic regression model. (DOCX 21 kb)

Abbreviations
EHR: Electronic Health Records; ICD: International Classification of Disease; NICE: National Institute for Health and Care Excellence; URTI: Upper Respiratory Tract Infection; WHO: World Health Organization

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
XS and RJ designed the study and participated in the elaboration of the protocol, LA and XS analyzed results and wrote the manuscript; LA participated in statistical analysis and wrote the manuscript; XS and RJ participated in fields and bench work; LA corrected manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate
The study was approved by the Committee for Research Ethics on Human Beings – PUCE (authorization CEISH-222-2016, 09th November 2016).

Consent for publication
Not applicable.

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

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Economic Evaluation

Medical Cost of Upper Respiratory Tract Infections in Children in Ambulatory Care

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ABSTRACT

Objective: The aim of this study was to estimate the direct cost per episode and the annual cost for upper respiratory tract infection (URTI) in children in Ambulatory Health Centers of the Ministry of Public Health (MSP) of Ecuador.

Methods: A cost of illness study with a provider perspective was carried out through a micro-costing of health resources and valuated in international dollars. Medical visits, laboratory tests, imaging examinations, and other procedures were valued using the tariff framework of services for the National Health System, and for prescribed medication a reported cost registry of pharmacy purchases made in the year of study was used.

Results: We included 380 electronic health records of children. We found a re-consultation rate of 22.89%, a medicine prescription rate of 95.52%, and an antibiotic prescription rate of 45.26%. The first medical consultation accounted for 71.9% of the total cost of URTI, the following visits accounted for 11.82%, and medication accounted for 14.68%. Antibiotics accounted for 58.92% of the total cost of medication.

Conclusion: The direct medical cost to the MSP of Ecuador of 1 episode of URTI in children in primary care was around I$37.28 (2017 dollars) (95% CI: I$35.81-I$38.75). The total cost of URTI cases in children to the MSP in 2017 was at least I$50.478 million (2017 dollars) (95% CI I$48.527m-I$52.523m). Re-consultation and the prescription of medication represent an important component of the direct cost of medical care of URTI.

Keywords: ambulatory care, cost, upper respiratory tract infection.

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Introduction

Common cold is a conventional term for a mild upper respiratory tract infection (URTI), usually a self-limited illness confined to the upper respiratory tract.[1] Common cold is a heterogeneous group of diseases caused by numerous viruses that belong to several different families; however, in some patients the viral infection predisposes to bacterial complications.

About 20% to 30% of colds remain without a proven viral cause. This could be explained because of the lack of availability of sophisticated diagnostic methods that can be applied in epidemiologic surveys and community based studies.[2] Children experience 3 to 8 colds per year, and 10% to 15% have at least 12 per year; these are usually associated with attendance at daycare centers or nurseries.[3]

Since URTI is caused by a multitude of different virus types with varying pathogenetic mechanisms, an effective treatment has not yet been developed. Symptoms such as rhinorrhea, sore throat, cough, fever, malaise, and myalgia are well known and last up to 10 days, although a lingering mucopurulent nasal discharge may persist for at least 2 weeks.[4] In infants, onset is more likely to be associated with a high fever, irritability, and nasal obstruction affecting feeding and sleep.

The symptomatic treatment of URTI has been aimed at relieving the most disturbing symptoms of the illness, and the recommendations come from low-quality studies, so variability of management exists among physicians.[5] Although antibiotics are not effective against viruses, they are widely used in the treatment of uncomplicated viral upper respiratory infections.[6-8]

URTI has typically been perceived as a self-limiting condition with little to no economic impact on the healthcare system. However, URTI is a very frequent reason for medical consult. It has been estimated that the consumption of resources for its treatment and diagnosis can be elevated, and the costs generated might inflict a great impact in the healthcare system.[9] URTI in children is the most commonly managed symptom in ambulatory care; almost 33% of children who are taken to a medical consultation have symptoms related to a common cold.[2,10] This is likely to generate a considerable cost burden to the healthcare system.

In Ecuador, the principal cause of ambulatory morbidity is acute nasopharyngitis.[11] No research to date has yet tried to estimate this cost burden on the healthcare system in Ecuador.

Demonstrating the importance of this issue to policy makers and clinicians would provide information to aid budgetary decision-making and insight into the need for interventions to reduce the future cost burden.

Materials and Methods

Objective

The aim of this study was to estimate the direct cost per episode and the annual cost of URTI in the Ambulatory Health Centers of the Ministry of Public Health (MSP) care system in 2017. Participants included children 1 to 18 years old who had been diagnosed with URTI.

Setting

Ecuador's health system is made up of 2 sectors, public and private. The public sector includes the MSP, the Ministry of Economic and Social Inclusion, the health services of the municipalities, and social security institutions (Ecuadorian Institute of Social Security, Institute of Security of the Armed Forces, and Social Security Institute of the National Police). The MSP is the governing body in health in the country, offering healthcare services to the entire Ecuadorian population; its financing comes from government contributions, and within the public health system it has a coverage of around 62%. Social security institutions cover the affiliated salaried population; their financing comes from economic contributions from the employer and the worker according to their remuneration. The Ecuadorian Institute of Social Security reaches a coverage of around 30.6%, and the other social security institutions have an approximate coverage of 7%. The private sector includes for-profit entities (hospitals, clinics, dispensaries, doctor's offices, pharmacies, and prepaid medicine companies) and nonprofit organizations of civil society and social service, whose coverage is usually for a population group with the other subsystems but that has the ability to pay.[12-14]

District 17D03 of the city of Quito belongs to the public health network of Ecuador. This district has a total assigned population of 430 000 inhabitants, and almost 36% is pediatric population (0-18 years). The district has 108 health workers, distributed in 22 ambulatory medical care centers, of which 19 are type A establishments (population assigned up to 10 000), 1 is type B (population assigned up to 25 000), and 2 are type C (assigned population up to 50 000). These health centers are distributed in rural and urban areas of the city and offer health services to 85% of the population.[14,15]

Sample

A simple probabilistic type sampling was performed. To calculate the sample, the total number of cases registered by URTI in the pediatric population reported by the MSP in the district in 2017 was used. The following formula was applied to calculate the sample for a finite universe, $n = N^{*}Z^{2*}p^{*}q \;/\; d^{2*}(N-1) + Z^{2*}p^{*}q$, where N is population size, Z is the confidence level (95%), p is the probability of success or expected proportion (50%), q is the probability of failure (50%), and d is precision (5% of maximum admissible error in terms of proportion). We decided to increase the sample by 10% considering possible losses. The subsequently studied sample comprised 380 electronic health records (EHR).

The inclusion criteria were patients between 1 and 18 years of age who required clinical care for URTI in the Ambulatory Health Centers of the MSP in the District 17D03 in 2017. The exclusion criteria were as follows: (1) patients who received clinical care in the ambulatory health centers of the MSP that are not a part of the D1703 district; and (2) patients who received clinical care in ambulatory health centers that are not a part of the MSP in the D1703 district.

The patients included in this study were those attended by the 5 types of health professionals who work in the designated health center and who diagnosed patients with URTI. These health professionals are classified as:

- Rural medical trainees: Medical doctor who has recently completed their degree and is performing a year of community service as a health professional in a rural location as a prerequisite for medical practice in Ecuador.
- General practitioner: Medical doctor who has completed the year of community service as a health professional and can practice medicine freely in Ecuador.
- Postgraduate medical student: Medical doctor who is studying a postgraduate course of 3 years in family medicine.
- Family medicine doctor: Medical doctor who has performed a postgraduate degree of 3 years in general practice and is considered a specialist in Ecuador.
- Pediatrician doctor: Medical doctor who has performed a postgraduate degree of 3 to 4 years in pediatrics and is considered a specialist in Ecuador.

Identification of Resource Use and Data Collection

Perspective

The provider perspective included all resources supplied by the MSP and used by participants during the period between the index consultation and resolution up to a maximum of 4 weeks following the initial consultation. This includes medical care, tests, diagnosis, and medication as principal resources. The International Classification of Disease (ICD)–10 was used for selection of the diagnosis criteria for URTI, where we considered codes J00-J06, J10, J11, H65, and H66 (Table 1).

Data source

The data source for the resources use and data collection included in this study were the EHR of all the patients from 1 health center of the Ministry of Public Health in the District 17D03 in Ecuador during 2017 with URTI as a primary diagnosis. This district has been using EHR since 2010. Prescribers enter the information directly into the EHR on a computer during the outpatient appointment. Information was manually extracted from the EHR simultaneously by 2 peer reviewers. The solicited tests and the administered medication were verified with the laboratory and pharmacy records from this medical institution.

Valuation of resources

All resources were valued in dollars at 2017 prices. Resource use was valued using recognized sources of unit costs; unit costs and their source are given in Table 2. Medical visits, laboratory tests, imaging examination, and other procedures were valued using the tariff framework of services for the National Health System,[16] and for prescribed medication a reported cost registry of pharmacy purchases made in the year of study was used. In the event that the pharmacy purchases records were not available, the information provided by the Technical Secretariat of Drug Pricing was included.[17] No discounting was necessary because the time period involved was 1 year. For monetary values to be comparable internationally, they were converted into international dollars (I$) using the purchasing power parity (PPP) conversion factor of Ecuador, which was 0.523 for the year 2017.[18]

Estimating the Annual Cost to the MSP

The estimated cost per episode to the MSP obtained from the cost-of-illness study was combined with the total number of episodes of URTI registered by the MSP in primary care to estimate the annual cost to the MSP system. The annual population cost was calculated as follows:

(cost per episode per child consulting) × *(total number of episodes per annum 2017)*

The number of episodes per annum is the number of children consulting with an URTI in a primary health center of the MSP according to Table 1 taken from the official of national statistics of 2017.[11] All analyses were carried out using SPSS v. 25 software.

Results

Participant Characteristics

Three hundred and eighty eligible EHR were randomly selected and proofed for suitability for inclusion in the cost-of-illness study. The general characteristics of our sample are described in Table 3.

Our sample of children contained more girls (50.3% vs 49.7%), and the mean of age was 4.73 years old. Out of 380 EHR, we found predominantly pediatrician consultations with 55.8% (212/380) followed by general practitioner consultations with 35.8% (136/380). Diagnostic labels most assigned by the 5 type of professionals were: acute nasopharyngitis (common cold) in 47.6% (181/380) of the cases, acute upper respiratory infections of multiple and unspecified sites with 16.6% (63/380), and acute pharyngitis with 14.7% (56/380) (Table 4).

Resource Use

The total resource use in the sample, by item, is given in Table 5. All children (380) had 1 primary care contact, and the re-consultation rate was 22.89% (87/380), but the total number of further consultations was 125. Out of these, 59 children needed 1 re-consultation (47.2%), 40 (32%) needed 2 re-consultations, 18 (14.4%) needed 3 re-consultations, and 8 (6.4%) needed 4 re-consultations.

Prescriptions were issued to 363 (95.52%) children, with 172 receiving antibiotics, constituting an antibiotic prescription rate of 45.26%; 631 units of antibiotics were used. The most dispensed antibiotic was amoxicillin 78.9% (498/631), azithromycin represented 9.8% (62/631), clarithromycin 7.45% (47/631), benzathine penicillin 2.2% (14/631), and other antibiotics constituted 1.5% (10/631).

Out of 363 children with prescriptions, 282 (74.21%) received an anti-inflammatory, which represented 979 units of anti-inflammatory/analgesic dispensed. The most prescribed anti-inflammatory was paracetamol at 50.9% (498/979), ibuprofen represented 48.6% (476/979), and diclofenac constituted a mere 0.5% (5/979). The resource use of other medication is included in Table 5.

A total of 98 laboratory tests were conducted in 49 children, from which 43 (43.9%) were blood count, 27 (27.55%) urine tests, and 28 (28.57%) stool tests. Additionally, 21 imaging exams were applied to 12 patients, resulting in 9 (42.85%) cavum x-ray, 10 (47.62%) sinus x-ray, and 2 (9.52%) chest x-ray. Fourteen therapeutic procedures (inhalation therapy) were conducted (Table 5).

Cost per Episode

The mean cost per child per each resource used is given in Table 5. Including the initial consultation and during the period before URTI resolution, the mean cost to the MSP per child was I$37.28 (2017 dollars) (95% CI I$35.81-I$38.75).

The mean cost to the MSP per child in the cases that required just 1 consultation was I$31.289 (2017 dollars) (95% CI I$30.53-I$32.02), and the mean cost per child in the cases that required 2 or more re-consultations was I$57.248 (2017 dollars) (95% CI I$53.72-I$60.76). We found a significant difference between these mean costs, MD 25.965 (95% CI I$22.31-I$28.31, $P<.0001$).

The mean cost of imaging tests used was I$9.665 (2017 dollars), and the mean cost of drugs prescription was I$5.717 (2017 dollars), accounting for 25.89% and 15.33% of the cost per child per episode, respectively. Therapeutic procedures and laboratory tests accounted for 13.79% and 4.87% of the mean cost per child, respectively.

Overall Cost

Overall cost for the whole sample is given in Table 5. The total cost of URTI for the whole sample was I$14 154.493 (95% CI I$14 133.541-I$14 175.445) (2017 dollars). The first consultation accounted for 71.9% of the total cost for the sample, and the subsequent consultations accounted for 11.82%.

The mean cost of URTI to the MSP for all cases that required just 1 consultation was I$9167.785 (2017 dollars) (95% CI I$8948.929-I$9386.634), and the mean cost per child in the cases that required 2 or more re-consultations was I$4980.581 (2017 dollars) (95% CI I$4674.627-I$5286.539). We found a significant difference between these mean costs, MD 2189.91 (95% CI I$4565.831-I$2808.413, $P<.0001$).

Table 1. ICD-10 codes considered "upper respiratory tract infections" for the purpose of this study.

We considered an upper respiratory tract infection diagnosis to be any diagnosis registered according to the ICD-10 classification, as any the following:
J00 Acute nasopharyngitis [common cold]
J01 Acute sinusitis *(includes J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, J01.9)*
J02 Acute pharyngitis *(includes J02.0, J02.8, J02.9)*
J03 Acute tonsillitis *(includes J03.0, J03.8, J03.9)*
J04 Acute laryngitis and tracheitis *(includes J04.0, J04.1, J04.2)*
J05 Acute obstructive laryngitis [croup] and epiglottitis
J06 Acute upper respiratory infections of multiple and unspecified sites *(includes J06.0, J06.8, J06.9)*
J10 Influenza due to other identified influenza virus (includes J10.1)
J11 Influenza due to unidentified influenza virus (includes J11.1)
We will consider, as part of the upper respiratory tract infections, diseases of the middle ear categorized according to ICD-10 as:
H65 Nonsuppurative otitis media
H66 Suppurative and nonspecified otitis media

ICD indicates International Classification of Disease.

Table 2. Source and value of unit costs.

Medical consultations	I$	Source
First consult	26.76	Tariff framework of services for the National Health System 2014
Re-consultation	13.38	Tariff framework of services for the National Health System 2014
Medication		
Azithromycin tablet 500 mg	0.172	Cotocollao Pharmacy 2017 expenditure voucher 323
Azithromycin syrup 200 mg/5 mL	0.841	Cotocollao Pharmacy 2017 expenditure voucher 323
Amoxicillin capsules 500 mg	0.095	Cotocollao Pharmacy 2017 expenditure voucher 323
Amoxicillin bottle 250 mg/5 mL	4.24	Cotocollao Pharmacy 2017 expenditure voucher 323
Amoxicillin/clavulanic acid syrup 250/62.5 mg/5 mL	2.58	Cotocollao Pharmacy 2017 expenditure voucher 323
Amoxicillin/clavulanic acid tablets 500/125 mg	0.592	Cotocollao Pharmacy 2017 expenditure voucher 323
Clarithromycin tablets 500 mg	0.592	Cotocollao Pharmacy 2017 expenditure voucher 323
Clarithromycin syrup 250 mg/5 mL	10.74	Cotocollao Pharmacy 2017 expenditure voucher 323
Cefalexin 250 mg/5 mL	0.86	Cotocollao Pharmacy 2017 expenditure voucher 323
Cefalexin capsules 500 mg	0.08	Cotocollao Pharmacy 2017 expenditure voucher 323
Tobramycin eye drops	10.43	Cotocollao Pharmacy 2017 expenditure voucher 323
Benzathine penicillin 1 200 000 UI	0.323	Cotocollao Pharmacy 2017 expenditure voucher 323
Benzathine penicillin 2 400 000 UI	1.816	Cotocollao Pharmacy 2017 expenditure voucher 323
Diclofenac 50 mg tablet	0.028	Cotocollao Pharmacy 2017 expenditure voucher 323
Diclofenac 75 mg ampoule	0.497	Cotocollao Pharmacy 2017 expenditure voucher 323
Ibuprofen 400 mg tablet	0.023	Cotocollao Pharmacy 2017 expenditure voucher 323
Ibuprofen 200 mg/5 mL syrup	2.045	Cotocollao Pharmacy 2017 expenditure voucher 323
Paracetamol 500 mg tablets	0.035	Cotocollao Pharmacy 2017 expenditure voucher 323
Paracetamol 100 mg/mL drops	0.420	Cotocollao Pharmacy 2017 expenditure voucher 323
Paracetamol 120 mg/5 mL syrup	0.207	Cotocollao Pharmacy 2017 expenditure voucher 323
Paracetamol 160 mg/5 mL syrup	0.395	Cotocollao Pharmacy 2017 expenditure voucher 323
Loratadine 10 mg tablets	0.066	Cotocollao Pharmacy 2017 expenditure voucher 323
Loratadine 5 mg/5 mL syrup	0.573	Cotocollao Pharmacy 2017 expenditure voucher 323
Ambroxol syrup	11.453	Technical Secretariat of Drug Pricing 2017
Ambroxol drops	5.105	Technical Secretariat of Drug Pricing 2017

continued on next page

Table 2. Continued

Medical consultations	I$	Source
Abrilar syrup	11.453	Technical Secretariat of Drug Pricing 2017
N-acetylcysteine ampoule	3,766	Technical Secretariat of Drug Pricing 2017
Loratadine/ambroxol syrup	15.755	Technical Secretariat of Drug Pricing 2017
Prednisone tablet 5 mg	0.152	Cotocollao Pharmacy 2017 expenditure voucher 323
Prednisone syrup 20 mg/5 mL	18.986	Technical Secretariat of Drug Pricing 2017
Dexamethasone 4 mg/2 mL ampoule	0.592	Cotocollao Pharmacy 2017 expenditure voucher 323
Betamethasone 4 mg/mL ampoule	0.248	Cotocollao Pharmacy 2017 expenditure voucher 323
Salbutamol spray 100 mcg/dosis atomization	2.007	Cotocollao Pharmacy 2017 expenditure voucher 323
Salbutamol solution 5 mg/mL inhalation	9.560	Cotocollao Pharmacy 2017 expenditure voucher 323
SRO envelope	0.803	Cotocollao Pharmacy 2017 expenditure voucher 323
Physiological serum bottle	3.078	Technical Secretariat of Drug Pricing 2017
Bromchovaxon capsules children	1,682	Technical Secretariat of Drug Pricing 2017
Kid cal syrup	32.944	Technical Secretariat of Drug Pricing 2017
Clotrimazole vaginal cream 2%	0.688	Cotocollao Pharmacy 2017 expenditure voucher 323
Tinidazole 1 g tablet	0.080	Cotocollao Pharmacy 2017 expenditure voucher 323
Zinc oxide topical cream	3.005	Cotocollao Pharmacy 2017 expenditure voucher 323
Laboratory		
Blood count	0.803	Tariff framework of services for the National Health System 2014
Urine elemental and microscopic	0.898	Tariff framework of services for the National Health System 2014
Gram and fresh drop	0.420	Tariff framework of services for the National Health System 2014
Coprological test	0.860	Tariff framework of services for the National Health System 2014
Serial coprological test	1.529	Tariff framework of services for the National Health System 2014
Imaging		
X-ray cavum	5.08	Tariff framework of services for the National Health System 2014
X-ray cavum and paranasal sinuses	11.319	Tariff framework of services for the National Health System 2014
X-ray thorax standard	3.843	Tariff framework of services for the National Health System 2014
X-ray paranasal sinuses	6.233	Tariff framework of services for the National Health System 2014
Procedures		
Inhalation therapy session	1,472	Tariff framework of services for the National Health System 2014

I$ indicates international dollars 2017.

Table 3. Characteristics of the sample.

Sample	n (%)	p
Health professionals	24 (100)	<0.0001
Rural trainee consultations	14 (4.5)	
General practitioner consultations	136 (35.8)	
Postgraduate medical student consultations	3 (0.8)	
Family medicine doctor consultations	12 (3.2)	
Pediatrician consultations	212 (55.8)	
Gender of patients		0.918
Female	191 (50.3)	
Male	189 (49.7)	
Age of patients		
Mean (SD)	4.73 (4.3)	<0.0001
Total of EHR	380 (100)	

EHR indicates electronic health records.

Drugs prescription accounted for 14.67% (I$2077.724) (2017 dollars) of the overall cost. Antibiotics accounted for 58.92% of the total cost of medication (I$1224 645) (2017 dollars). Cost by type of antibiotics is shown in Table 6. Beta-lactam type antibiotics were the most antibiotic dispensed for URTI with 81.45% (514/631), and macrolides counted for 17.27% (109/631). Among beta-lactam antibiotics, amoxicillin (including all pharmaceutical presentations) was the most dispensed of them with 96.88% (498/514) units dispensed, and it counted for 64.16% of the overall cost of antibiotics. Among macrolides, azithromycin was the most dispensed at 56.88% (62/109), and it counted for 1.36% of the overall cost of antibiotics. Clarithromycin was the least prescribed among the macrolides at 43.11% (47/109), but it counted for 27.14% of the overall cost of antibiotics.

Therapeutic procedures, laboratory tests, and imaging tests all accounted for 1.6% of the overall cost (I$228.679) (2017 dollars).

Annual Cost to MSP

We combined the cost per episode results with data on prevalence. The number of consultations for URTI in the ambulatory health centers of the Ministry of Public Health in 2017 was 1 355 165.[11] Thus, the annual cost to the MSP was at least I$50.478 million (2017 dollars) (95% CI I$48.527m-I$52.523m).

Sensitivity Analysis

The results coming from the cost-of-illness study may be conservative; the effect of the antibiotic prescription rate is explored here. We found a higher rate of antibiotic prescription in the temporality of study compared to other regional countries (24%-40%) and even compared to national data (36%). Using an antibiotic prescription rate of 35%, which may be more realistic according to national data, the population cost estimate would result in almost the same sum, I$49.90 million (2017 dollars); but if we considered regional data about antibiotic prescription rate in URTI, around 30%, the population cost estimate would be significantly lower, I$42.82 million (2017 dollars). Other variables in the study do not affect greatly the results as we found a relative low use of complementary exams for diagnosis and treatment for URTI, expected for a clinical condition that generally does not require laboratory tests and imaging.

Discussion

Resource Use and Cost per Episode

Our study estimates the medical care cost for URTI from medical records with diagnosis that have been codified according to the ICD-10, and from the information of the use of resources from pharmacy, imaging, and laboratory. This type of costing allows us to obtain a more precise estimate sum. One of the advantages of the present study is that the applied methodology for the estimation follows micro-costing. Micro-costing is a cost estimation method that involves the “direct enumeration and costing out of every input consumed in the treatment of a particular patient”; this improves precision in cost estimation and reflects actual resource use and economic costs by collecting detailed data on resources used and the unit costs of those resources.[19]

Medical care and re-consultation represent 20.44% of the use of resources per URTI episode. All children had at least an initial consultation, and the rate of re-consultation was 22%; this figure agrees with the expected range from 17% to 24% proposed in the consulted literature.[20,21] Prescription of medicine is the most used resource in the treatment of URTI cases. It accounts for 74.1% of all the administered units of resources, which corresponds to a rate of prescription of 95.52%. This number is similar to other studies where the rate is situated between 70% and 90% in children.[22] Anti-inflammatory drugs and antibiotics were the most prescribed drugs, a statistic that is similar to other different ambulatory studies.[23-25] The rate of prescription for antibiotics was 45.26%. This number resulted in being higher when compared to the one obtained by our previous study in Ecuador from 2015, where the rate of prescription for antibiotics in children with URTI diagnosis was 36.9%,[7] and higher compared with regional data, in a study from 2016[8] where, in 4 Latin American countries, patients with a suspected diagnosis of URTI in primary care health centers reported an antibiotic prescription rate of 35% in Argentina, 40% in Bolivia, 24% in Paraguay, and 27% in Uruguay. These differences might be related to knowledge, attitude, and how medical practitioners prescribe drugs.[26-28] The use of complementary tests was low (<5%), which is very similar to what is found in specialized literature related to the use of resources for the diagnosis of URTI.[29]

The direct medical cost of 1 URTI episode in primary care in children in the MSP of about I$37.28 (2017 dollars) is significant. The cost of the first medical consultation was I$26.76 (2017 dollars), which means that almost 72% of the cost came only from the medical appointment. Added to this, a subsequent medical evaluation, which is a medical strategy used to closely evaluate particular cases of URTI, cost I$19.23 (2017 dollars) per patient, so in those particular cases of URTI the cost of the medical appointment can be increased by 71%. Therefore, it is important to establish specific indications to proceed with that strategy in order to maintain a relative low rate of re-consultation and contain costs; nevertheless, it is important to mention that our study tried to identify possible areas for interventions in terms of cost containment, but it is necessary to carry out adequate cost-effectiveness studies to make an adequate decision. Medication prescriptions represents 14.66% of the total cost of URTI, and antibiotics account for 58.94% of the cost of all prescribed medication.

Annual Cost to MSP

Cost-of-illness studies can be described as prevalence-based or incidence-based approaches, based on how the epidemiological data are used.[30] The prevalence-based approach can be particularly useful when the main study purpose is to design cost

Table 4. Diagnosis of URTI cases by each type of health professional.

Health professional	ICD-10 diagnosis n (%)									
	J00	J01	J02	J03	J04	J05	J06	H65	H66	Total
Rural Medical Trainee	13 (76.4)	0 (0)	3 (17.7)	0 (0)	0 (0)	0 (0)	1 (5.9)	0 (0)	0 (0)	17 (4.5)
General Practitioner	76 (55.9)	4 (2.9)	21 (15.4)	27 (19.9)	1 (0.74)	1 (0.74)	3 (2.2)	1 (0.74)	2 (1.5)	136 (35.8)
Postgraduate Medical Student	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.8)
Pediatrician Doctor	85 (40.1)	21 (9.91)	31 (14.6)	9 (4.2)	6 (2.8)	1 (0.5)	56 (26.4)	3 (1.4)	0 (0)	212 (55.7)
Family Medicine Doctor	6 (50.0)	0 (0)	0 (0)	3 (25.0)	0 (0)	0 (0)	3 (25.0)	0 (0)	0 (0)	12 (3.2)
Total	181 (47.6)	25 (6.6)	56 (14.7)	40 (10.5)	7 (1.8)	2 (0.5)	63 (16.6)	4 (1.1)	2 (0.5)	380 (100)

J00 Acute nasopharyngitis [common cold], J01 Acute sinusitis, J02 Acute pharyngitis, J03 Acute tonsillitis, J04 Acute laryngitis and tracheitis, J05 Acute obstructive laryngitis [croup] and epiglottitis, J06 Acute upper respiratory infections of multiple and unspecified sites, H65 Nonsuppurative otitis media, H66 Suppurative and nonspecified otitis media.

Table 5. Total resource use and cost per episode per participant.

Direct sanitary resources	Number of patients	Units dispensed	Mean cost per child (SD)	Overall cost (SD)
First consultation	380	380	26.768 (0)	10172.084
Re-consultations	87	125	19.23 (9.732)	1573.04
Therapeutic procedures	14	14	5.143 (0.841)	20.611
Laboratory tests	49	98	1.816 (0.994)	92.275
Imaging tests	12	21	9.655 (2.829)	115.793
Prescriptions	363	1832	5.717 (7.036)	2077.724
Antibiotics	172	631	7.112 (5.927)	1224.646
Anti-inflammatory	282	979	1.185 (1.147)	333.441
Mucolytics/antitussives	39	39	3.652 (2.562)	142.600
Antihistamines	69	108	0.726 (1.223)	49.770
Others	38	75	8.604 (9.483)	327.265
Total cost			37.284 (14.722)	14154.493

Cost presented as international dollars 2017.
SD indicates standard deviation.

Table 6. Cost by type of antibiotics.

Type of antibiotic	Units	Total cost	%
Amoxicillin capsules 500 mg	92	8.80	0.72
Amoxicillin bottle 250 mg/5 mL	157	666.42	54.42
Amoxicillin/clavulanic acid syrup 250/62.5 mg/5 mL	30	77.44	6.32
Amoxicillin/clavulanic acid tablets 500/125 mg	219	33.08	2.70
Azithromycin syrup 200 mg/5 mL	9	7.57	0.62
Azithromycin tablet 500 mg	53	9.12	0.74
Cefalexin 250 mg/5 mL	2	1.72	0.14
Clarithromycin syrup 250 mg/5 mL	30	322.37	26.32
Clarithromycin tablets 500 mg	17	10.08	0.82
Benzathine penicillin 1 200 000 UI	14	4.52	0.37
Tobramycin drops 0.3%	8	83.52	6.82
Total	631	1224.24	100

Cost presented as international dollars 2017.

containment policies; this approach provides decision makers with the major cost components, which are the areas where cost containment policies would have the greatest impact.[31]

The total cost of URTI in children to the MSP in 2017 was around I$50.478 million. If antibiotic use had been 50% lower, our estimate of cost per episode would be I$1.64 (2017 dollars) lower and the annual cost to the MSP reduced by I$2.29 million (2017 dollars). Additionally, if the use of other medicines such as cough suppressants, mucolytics, and so forth was lower, due to its lack of efficiency in the treatment of URTI in children,[5,32,33] our estimate of cost per episode would be I$1.85 (2017 dollars) lower and the annual cost to MSP reduced by I$3.93 to I$46.65 million (2017 dollars). Therefore, an intervention that promotes rational antibiotic prescription and disuse of ineffective drugs in URTI (eg, mucolytics or cough suppressants) would be cost saving.

The MSP budget for 2017 was I$5148.23 million, of which 82.61% was allocated to the "provision of health services," that is, around I$4252.73 million.[34,35] The costs associated to URTI in children are significant; URTI was the first cause of morbidity in outpatient care in 2017,[11] and in this age group the overall cost represented at least 1.19% of the assigned budget.

A limitation of this study is that it only estimates the direct medical costs of the subsidized population of the MSP. Nevertheless, the obtained results from a provider perspective can enable and help to design cost containment policies, with the goal being the improvement of the efficiency of use of resources in medical care. Another advantage is that URTI cases were selected based on the ICD-10 registration in the EHR; this allowed for the obtaining of precise data related to the use of resources. Direct medical costs of URTI represent an important economic burden on the subsidized public health system of Ecuador; our findings highlight the need for further studies in the evaluation of the social economic costs of URTI.

Conclusion

The medical cost to the MSP of Ecuador of URTI in children in primary care is considerable. Re-consultation and antibiotics represent important components of the direct cost of medical care of upper respiratory tract infection. Cost containment policies that are focused on appropriate prescription and rational use of antibiotics in URTI episodes can be cost saving.

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Knowledge, Attitudes and Practices in Antibiotic Use in Family Medicine Students

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Abstract

Background: Inappropriate prescriptions of antibiotics lead to ineffective and unsafe treatments and worsening of diseases. Medical students may have deficiencies in their prescription skills and they may need further training in the use of antibiotics for their practice. Medical skills in prescribing antibiotics can be improved through continuous medical education. The aim of this study was to assess the current levels of knowledge, attitudes, and practices (KAP) in antibiotic prescription in upper respiratory tract infections (URTI) among postgraduate family medicine students in Ecuador. **Methods:** A cross-sectional study with an on-line survey, based on micro-curricular contents, to evaluate KAPs regarding antibiotic prescription in URTI among postgraduate family medicine students in 5 provinces of Ecuador. **Results:** Two hundred and seventy-three physicians responded (94.1%). Most physicians treated between 1 and 5 URTI cases per day. The odds for inadequate knowledge and inappropriate practices in URTI among postgraduate family medicine students were 8.74 (95%CI, 4.94-15.46, $P < .001$) and 5.99, (IC95%, 2.66-13.50, $P < .001$) in physicians who were students of the first half of the study program. **Conclusion:** The knowledge in URTI was limited among physicians. Nonetheless, they expressed a positive attitude toward not using antibiotics in URTI. A postgraduate program can significantly improve the knowledge and practices related to antibiotic prescriptions in URTI.

Keywords

primary care, community health, antibiotic use, medications, respiratory infection

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Background

Inappropriate antibiotic prescription is an increasing problem among physicians in several low- and middle-income countries and it increases the risk of patients developing antibiotic-resistant microorganisms.[1,2] Antibiotic use occurs commonly in primary care in upper respiratory tract infections (URTI).[3] Regardless of the fact that the majority of URTIs are caused by viruses, antibiotics are still being prescribed for maladies such as common colds, acute rhinitis, or acute bronchitis.[4-7]

There are healthcare provider factors strongly associated with the prescribing behavior. Studies have shown that provider factors like age, gender, medical specialty, sociodemographic group, and previous personal experiences can influence in the prescription of antibiotics in primary care.[8] Factors like patient's demands, health provider's knowledge, use of clinical guidelines, professional experiences, treatment failure, and availability of drugs can also be mentioned as relevant factors for inappropriate antibiotic prescribing.[9,10] Furthermore, factors related to physical exams have also been associated with physicians' decisions of using antibiotics. In URTI cases, the findings of fever, purulent sputum, abnormal respiratory exams, and tonsillar exudate in the physical examination can also influence the decision to prescribe antibiotics.[11] Prescribing behavior is influenced by the physician's own knowledge, personal experiences, and cultural factors.

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In Latin American countries, the rate of antibiotic prescription in URTIs is between 24% and 40%.[12,13] The antibiotic prescription rate in URTIs in Ecuador is around 37.5%; however, 90.25% of these prescriptions made by physicians are unnecessary.[14] As per Ecuadorian healthcare laws, antibiotics are only sold under medical prescription and since physicians are responsible for this practice, it is necessary to assess the knowledge, attitudes, and practices (KAP) that underlie their prescribing behaviors. Physicians may have deficiencies in prescription skills and they may need more training in antibiotic use for their practice.[15-17]

Ecuador has many educational programs in Family Medicine. Currently, they are taught in twelve provinces in medical schools and these programs are aligned with the country's healthcare model.[18] Because medical skills in antibiotic prescription can be improved through continuing medical education,[19,20] it is important to explore whether a postgraduate program in family medicine could improve KAPs in antibiotic prescription in URTI cases in Ecuador.

Methods and Materials

Study Design and Population

This is a cross-sectional study which applied a survey to asses KAPs among postgraduate family medicine students of the Pontifical Catholic University of Ecuador (PUCE). The students have their clinical practice in 5 provinces of Ecuador (Esmeraldas, Imbabura, Manabí, Pichincha, and Santo Domingo de los Tsáchilas). These provinces correspond to the coastal and mountainous regions of Ecuador. A total of 290 students of the Family Medicine Program were chosen to participate in the survey. The survey was sent by e-mail to 290 students of the Family Medicine Program from October 2019 to December 2019; students were able to accept or decline participation in the study, the students had to accept an informed consent form before taking the survey.

Questionnaire

An on-line self-administered questionnaire was developed in order to evaluate KAPs about antibiotic prescription in URTI cases among students in the Family Medicine Program. The 18 questions were developed according to the micro-curricular contents of the program. The survey used a mixed questionnaire which included multiple-choice questions and Likert scales (1 = never, 2 = almost never, 3 = half the time, 4 = almost always, 5 = always) to explore KAPs in URTI cases. The questionnaire covered a broad range of domains which aimed to assess participants KAPs, including basic knowledge of URTI and antibiotic prescription practices. The survey was validated by an advisory committee integrated by family physicians, professors of the family medicine program and faculty experts. After validation, the survey was tested among general practitioners that were not included in the study. A total of 18 questions were used to assess KAP, 8 for knowledge, 5 for attitudes, and 5 for practices.

Data Analyses

Data were anonymously entered into the Statistical Package for Social Sciences (SPSS, version 21, Chicago, IL, USA) and a descriptive analysis was conducted. The analysis of categorical and continuous variables was carried out using proportions and means, respectively. A Cronbach's alpha test was conducted to assess internal reliability, the alpha score was 0.75, indicating a moderate level of reliability of the questionnaire.[21]

A scoring system was applied to measure the respondents' KAPs toward to prescription of antibiotics in URTI cases. The scores were calculated as a continuous variable by summing the participant's correct responses to each question. A 2-level category was established and 60% of the correct answers in each domain were taken as a discrimination value. Scores in knowledge were categorized into adequate and not adequate; meanwhile, scores in attitude were classified into conservative and not conservative and the scores in practices as appropriate and not appropriate. Statistical tests helped determine the association between each score category and several variables through a logistic regression. This type of regression analyzed the relationship between a dependent variable, scores of each KAP domain and some independent variables, controlling for potential confounders. The independent variables were chosen by theoretical relationship to the dependent variable and through a bivariate logistic regression model. All variables with $P < .25$ in the univariate analysis were included in the multivariate logistic regression analysis to determine the factors that were independently associated with each of the 3 dependent variables. In order to choose among the models to be used, we used Akaike's Information Criteria (AIC).[22] The formulas for the final models in each KAP domain were:

$$Log(Klevel) = b0 + b1 * periodProg + b2 * gender + b3 * region$$

$$Log(Alevel) = b0 + b1 * periodProg$$

$$Log(Plevel) = b0 + b1 * periodProg$$

where *Klevel* refers to the level of knowledge of the interviewee, *periodProg* is the period of time of the family medicine program that the respondent had completed at the moment of taking the survey, *gender* is the gender of the student, and *region* is the geographic region. In addition, *Alevel* refers to the level of attitude and *Plevel* is the level of practice.

Table 1. Characteristics of the Sample.

Variable	n (%)
Gender	
Male	97 (35.53)
Female	176 (64.46)
Age Mean (SD)	31.1 (2.82)
Time (years) since the student graduated	6.2 (2.31)
Sector of practice medicine	
Public	200 (73.26)
Private	54 (19.78)
Public and private	19 (6.95)
Geographic region	
Coastal region	136 (49.81)
Mountainous region	137 (50.18)
Program period	
First half	132 (48.35)
Second half	141 (51.64)
Level of medical practice	
First level	186 (68.13)
Second level	63 (23.07)
Third level	24 (8.79)
Medical consultations per day	
1-5 patients/day	8 (2.93)
6-10 patients/day	57 (20.87)
10-15 patients/day	84 (30.76)
>15 patients/day	124 (45.42)
URTI cases per day	
1-5 cases	249 (91.20)
6-10 cases	20 (7.32)
10-15 cases	2 (0.73)
>15 cases	2 (0.73)
Attention time per patient	
≤15 minutes	18 (6.59)
15-30 minutes	251 (91.94)
>30 minutes	4 (1.46)

Abbreviations: SD, standard deviation; URTI, upper respiratory tract infection.

Results

The characteristics of the sample are shown in Table 1. A total of 273 students of the Family Medicine Program responded the survey, which represents a response rate of 94.1%. The responders were mainly women 64.5% (76/273) with an average age of 31.1 years old. Furthermore, 51.6% (141/273) of the students were in the second half of the program and most of them 68.1% (186/273) were working in primary care. 45.4% (124/273) of the participants indicated that they carried out more than 15 medical consultations per day and 91.2% (248/273) of them reported that they treated between 1 and 5 cases of URTI per day. Most physicians, 91.9% (251/273), took between 15 and 30 minutes per patient.

Evaluation of Knowledge

Eight questions evaluated basic knowledge in etiology, diagnosis, and treatment on URTI (Table 2). Questions KQ4 and KQ5 had the highest frequency of correct answers (71.1% and 67.4%, respectively); these questions evaluated the issues of etiology and diagnosis in URTI cases. However, other questions that evaluated similar topics, KQ6 and KQ7, had the lowest frequency of correct answers, 53.1% and 58.6%.

Questions that evaluated knowledge about the adverse effects of common drugs used in the treatment of URTIs, KQ3, and KQ8, had the lowest frequency of correct answers (24.2% and 30.8%, respectively). Additionally, the ones that evaluated treatment of choice and reasons to use antibiotics, KQ1 and KQ2, had a lower-than-expected number of correct answers (53.1%).

After evaluating all the answers from the knowledge questions, it became apparent that 45.4% (124/273) of the physicians achieved a score of at least 60%; and out of these, 76.6% (92/124) achieved a score greater than 75%.

Our final multiple logistic regression model included the level of knowledge as a dependent variable and the period of the program, gender, and geographic region as independent variables. We found a significant difference in level of knowledge for all the variables included in the model. Using the percentage of participants who were in the second half of the study program as the reference point for the study variable and holding the gender and geographic region variants constant, it became noticeable that the odds of inadequate level of knowledge among physicians of the family medicine program was 8.74 times greater in the physicians who were in the first half of the program period. When adjusting the model for gender and geographic region, the odds of inadequate level of knowledge was 1.99 times greater for female gender and 1.85 times greater for those who were working in the coast region (Table 3).

Evaluation of Attitudes

Five questions evaluated participants' attitudes toward the management of URTI cases (Table 2). All questions, except question AQ4, were answered in a majorly correct way, showing a conservative attitude toward antibiotic use in URTI cases. Question AQ4 evaluated participants' perception of accessible resources for education in the use of antibiotics in URTI cases. About 50.9% of physicians feel that there are insufficient resources.

After obtaining data from all of the questions that evaluated attitudes, it became evident that 77.7% (212/273) of physicians showed a conservative attitude toward antibiotic prescription. We did not find a significative relationship between the period of the program and participants' attitudes (OR: 1.46, IC95%, 0.82-2.59, $P = .192$).

Table 2. Questions of Knowledge, Attitudes, and Practices in URTI.

Knowledge questions	Correct n (%)	Incorrect n (%)
KQ1. Treatment of choice in GAS	145 (53.11)	128 (46.88)
KQ2. Prevention in complication in GAS	145 (53.11)	128 (46.88)
KQ3. Adverse effects of antibiotics used in URTI	66 (24.17)	207 (75.82)
KQ4. Etiology in AOM	194 (71.06)	79 (28.93)
KQ5. Criteria for use antibiotics in URTI	184 (67.39)	89 (32.60)
KQ6. Usefulness of laboratory test in URTI	145 (53.11)	128 (46.88)
KQ7. Criteria for use antibiotics in URTI	160 (58.60)	113 (41.39)
KQ8. Adverse effects of other drugs used in URTI	84 (30.76)	189 (69.23)
Overall score	124 (45.42)	149 (54.57)
Attitude questions	Conservative n (%)	Not conservative n (%)
AQ1. Views on delayed antibiotic prescription	199 (72.89)	74 (27.10)
AQ2. Decision for immediate antibiotic prescription	188 (68.86)	85 (31.13)
AQ3. Confident of antibiotic prescription	241 (88.327)	32 (11.72)
AQ4. Availability of information resources	134 (49.08)	139 (50.91)
AQ5. Decision for antibiotic prescription	199 (72.89)	74 (27.10)
Overall score	212 (77.65)	61 (22.34)
Practices questions	Appropriate n (%)	Not appropriate n (%)
PQ1. Frequency of antibiotic prescription decision	175 (64.10)	98 (35.89)
PQ2. Use of institutional prescription protocols	260 (95.23)	13 (4.76)
PQ3. Use of continuing medical education resources	202 (73.99)	71 (26.00)
PQ4. Use of clinical practice guidelines	261 (95.60)	12 (4.39)
PQ5. Decision-based way on prescription	66 (24.17)	207 (75.82)
Overall Score	230 (84.24)	43 (15.75)

Abbreviations: GAS, Group A *streptococcal pharyngitis*; URTI, upper respiratory tract infection; AOM, acute otitis media.

Evaluation of Practices

Five questions evaluated practices in the management of URTI cases (Table 2). All questions, except question PQ5, aimed to assess appropriate practices in antibiotic use in URTI cases. Question PQ5 evaluated decision making in antibiotic prescription, 75.8% (207/273) of physicians said that they do so based on experience.

After obtaining information from all the questions that evaluated practices, it became clear that 84.2% (230/273) of physicians showed appropriate practices. We found a significative relationship between the period of the program in which the participants were at the moment of answering the survey and their practices in antibiotic prescription (OR: 5.99, IC95%, 2.66-13.50, $P < .001$).

Discussion

This study is the first to explore physicians' KAPs in antibiotic prescription in URTI cases among physicians in Ecuador. It intends to ascertain whether a postgraduate program in family medicine could change KAPs in training physicians. The results demonstrate that knowledge in URTI cases and antibiotic prescription among junior physicians in Ecuador is limited but attitudes and practices related to the prescription of this kind of medicine are virtuous.

Our findings are similar to previous studies that show lack of knowledge in the prescription of antibiotics[23-25]; even though this study is among the first few to quantify it. Knowledge in URTIs among physicians was limited in this study, less than half of the responders had an adequate knowledge according to the survey. Although participants answered questions related to basic topics such as etiology adequately, questions with topics related to criteria, decision making, and treatment of choice were incompetent.

Antibiotic prescription has been proposed to be influenced by intrinsic prescriber factors; for instance, gender, years of practice, residence, and continuous medical education.[26] We found that gender and geographic region are factors related to antibiotic prescription in this particular group of physicians; nevertheless, other studies have not shown similar results in this aspect.[27,28] This result can be explained through the evidence suggesting that in Ecuador there are important cultural differences between regions and this factor could very easily influence the way in which a curriculum is implemented.[29,30]

Table 3. Odds Ratios for Inadequate Level of Knowledge in URTI.

Variable	Odds Ratio (95% CI)	*P*-value
Program period		
Second half (REF)	1.00	
First half	8.74 (4.94-15.46)	<.001
Gender		
Male (REF)	1.00	
Female	1.99 (1.10-3.60)	.022
Region		
Mountainous region (REF)	1.00	
Coastal region	1.85 (1.05-3.25)	.031

Abbreviations: URTI, upper respiratory tract infection; CI, confidence interval; REF, reference.

The identification of prescription-related factors is very important when designing interventions to improve the practices regarding the prescription of antibiotics.[31,32] Studies have confirmed that continuous medical education is an effective approach toward improving physicians' knowledge and prescription behavior.[33,34] Interventions can be classified by the level in which they would be applied, so there are interventions in the administrative level, patient level, and physician level. At the physician level, interventions include educational materials, group education, computer-assisted decision-making systems, form-filling control, restrictive form-filling processes, and financial incentives[34]; all of which focus on short- and medium-term interventions to achieve an improvement in the knowledge on antibiotic prescription practices. Consequently, a reduction in antibiotic use should be accomplished. We did not identify studies evaluating a postgraduate medical program for improving KAPs in prescribing antibiotics. Therefore, our study could be the first to show that a continuous medical education through a postgraduate program in family medicine would improve the knowledge about URTI cases and their correlation to antibiotic prescription in general practitioners.

Lack of knowledge and preparedness in general practitioners may be related to a limited exposure and preparation for clinical practice.[35] This situation could be improved by increasing the number of opportunities to develop the skills for prescribing drugs in a controlled and supervised environment. In postgraduate education, role models encourage active participation and teach advanced skills,[36] a postgraduate program in family practice offers those opportunities through a modelling teaching experience by an experienced doctor.

Studies that explore subjective perceptions that could influence antibiotic prescription are mostly qualitative. Due to their methodology, those studies are unable to establish a possible relationship or a magnitude of association between the two.[26] The present study explores aspects in decision-making in antibiotic prescription, delayed prescription, immediate prescription and availability of information resources. All the questions of the survey were answered adequately. Medical students show agreement with better stewardship toward the prescription of antibiotics, including strategies of a delayed antibiotic prescription or not prescribing antibiotics at all, showing that attitudes are relatively conservative. The establishment of an antibiotic stewardship program should be encouraged, as this has been proven to benefit in contributing to a more rational use of antibiotics. These strategies are effective in reducing the use of antibiotics for medical conditions where they are not advised or necessary.[37,38]

We found a fair score in practices among physicians and a significative relationship between the period of the program in which they were at the moment of the survey and their prescription practices. Although, we identified a discordance between the overall score and the specific question regarding decision-making related to prescriptions, most physicians answered that they do it based on experience but they use the appropriate tools in clinical practice. A study conducted in Singapore showed that physicians agreed to use clinical practice guidelines (CPGs) on the use of antibiotics in URTI cases; however, less than half of the consulted doctors expressed that those guidelines would not change their prescribing practices.[9] A study conducted by Solà et al[39] identified that physicians' perception of the usefulness of CPGs is affected by the disagreement between its theoretical content and the daily practice; therefore, the decision-making in clinical practice can differ from the objectives of CPGs. It can be hypothesized that tools like institutional protocols and CPGs are used by this group of physicians as a tool for diagnosis and to a lesser extent for decision-making in treatment options, because the lack of national CPG and the use of international guidelines may not support decision-making for treatments available in specific local contexts. Further studies are required to understand the perception of physicians regarding the usefulness of CPGs.

Self-reported data obtained by self-administered surveys can have limitations. Lack of comparability of the results with data on real scenarios should be considered because in this kind of surveys responders tend to answer correctly. Thus, reliability can be affected. Moreover, it was impossible to cross-check survey responses with actual prescription practices, hence the study might have incurred in social desirability bias.[40] Besides, it was unfeasible to establish the quality and quantity of antibiotic prescription. Other limitation is the use of convenience sampling with doctors from a single university, so our findings should be interpreted with caution when generalizing to all programs in the country, because we could have incurred in selection bias.

A strong point of this study was the high response rate achieved, as well as the design of a multiple-choice questionnaire as compared to other methods of measuring the degree of agreement in KAPs studies using only Likert scales. Furthermore, the content of the questionnaire was developed based on a micro-curricular program; consequently, it can be assumed that all physicians have been taught equally. Additionally, the survey tool was rigorously validated by experts and faculty members, and pretested among general practitioners to evaluate reproducibility, reliability, and consistency.

Given the very limited literature about the effect of postgraduate programs in medical education in KAPs, we believe this study adds value in understanding the topic. We recommend doing future studies in order to compare KAPs in real scenarios.

Conclusion

Knowledge in antibiotic prescription in URTI cases among family medicine students in Ecuador is limited. A postgraduate program in general practice can significantly improve the knowledge and practices related to antibiotic prescription in URTI cases. Future studies are needed to establish whether clinicians' KAPs influence the quality and quantity of antibiotic prescription.

Authors' Note

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Author Contributions

Concept and design: XS, AL, PL. Acquisition of data: AL, PL. Analysis and interpretation of data: XS, AL, PL. Drafting of the manuscript: XS, AM, RJ. Critical revision of the paper for important intellectual content: AM, RJ, AMo. Statistical analysis: XS, RJ. Provision of study materials or patients: AL, PL. Administrative, technical, or logistic support: XS, AM, RJ, AMo. Supervision: XS.

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Ethical Approval

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RESEARCH ARTICLE

Reducing unnecessary antibiotic prescription through implementation of a clinical guideline on self-limiting respiratory tract infections

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Abstract

Background

Clinical guidelines (CG) are used to reduce variability in practice when the scientific evidence is sparse or when multiple therapies are available. The development and implementation of evidence-based CG is intended to organize and provide the best available evidence to support clinical decision making in order to improve quality of care. Upper respiratory tract infections (URTI) are the leading cause of misuse of antibiotics and a CG may reduce the unnecessary antibiotic prescription.

Methods

The aim of this quasi-experimental, before-after study was to analyze the short- and long-term effects of the implementation of a CG to decrease the rate of antibiotic prescription in URTI cases in the emergency department of a third level private hospital in Quito, Ecuador. The study included 444 patients with a main diagnosis of URTI. They were distributed in three groups: a baseline cohort 2011 (n = 114), a first post-implementation cohort 2011 (n = 114), and a later post-implementation cohort 2018 (n = 216). The implementation strategy consisted of five key steps: acceptance of the need for implementation of the CG, dissemination of the CG, an educational campaign, constant feedback, and sustainability of the strategy through continuous training.

Results

The results of this study show a 42.90% of antibiotic prescription rate before the CG implementation. After the implementation of the CG, the prescription rate of antibiotics was significantly reduced by 24.5% (42.9% vs 18.4%, p<0.0001) and the appropriate antibiotic prescription rate was significantly increased by 44.2% (22.4% vs 66.6%, p<0.0001) in the first post-implementation cohort 2011. There was not a significant difference in antibiotic prescription rate and appropriate antibiotic prescription rate between two post-implementation cohorts: 18.4% vs 25.9% (p = 0.125) and 66.6% vs 50% (p = 0.191), respectively.

Conclusions

The implementation of CGs decreases the rate of antibiotic prescription in URTI cases. The results are remarkable after early implementation, but the effect persists over time. The emphasis must shift from guideline development to strategy implementation.

Introduction

Inappropriate antibiotic prescription practice is among the most commonly discussed public health issues. According to the World Health Organization (WHO), half of all prescribed medications are prescribed in an inappropriate way [1]. Medicines are considered appropriate to be prescribed to the general population when they have a clear, scientific evidence-based indication, are well tolerated in the majority of patients and are cost-effective [2–4]. In addition, a rational use of medications requires that patients receive medications appropriate to their clinical needs.

The common cold is a generic term used to describe a form of mild upper respiratory tract infections (URTIs) caused predominantly by viral pathogens [5]. Actually, the common cold is a heterogeneous group of diseases caused by numerous viruses that belong to several families. However, a viral infection predisposes some patients to bacterial superinfections. About 20–30% of cold symptoms remain without a proven viral cause [6]. This could be explained because of the lack of availability of sophisticated diagnostic methods that can be applied in epidemiological surveys and community-based studies.

The symptomatic treatment of URTI has been aimed at alleviating the most uncomfortable symptoms of the disease. Part of the treatment recommendations about using some medications stem from low-quality studies, so there is variability in treatment among healthcare providers [7]. Although antibiotics are not effective against viruses, they are widely used in the treatment of uncomplicated viral URTI cases [8, 9].

Studies have shown that factors like age, gender, medical specialty, sociodemographic and previous personal experiences can influence a physician's decision to prescribe antibiotics in primary care [10]. The prescription of an antibiotic is influenced by the patient's demand and expectations, the health care provider's knowledge of evidence-based medicine, current guidelines, years of professional experience, lack of knowledge about the proper use of antimicrobials, complacency with the patient, provider's fear to fail to treat the patient's illness, and lack of time or availability of drugs [11]. Thus, the prescription of an antibiotic is influenced by factors that affect all stakeholders, including physicians, other health care providers, the health system, and patients. These factors are mutually related [12]. On the other hand, factors related to symptoms found in physical exams such as fever, purulent sputum, abnormal respiratory exam, and tonsillar exudate, have also been associated with antibiotic prescription in URTI cases; as health care providers believe that they are more indicative of a bacterial etiology [13].

Various strategies have been proposed to reduce inappropriate antibiotic prescription in URTI cases. The most studied interventions are educational materials for physicians, audits and feedback, educational meetings, changes in the financial and healthcare systems, reminders, electronic assistance systems, patient-target interventions, and multifaceted physician-target interventions [14–16]. Among all the interventions, those that include educational material for doctors and parents, were the most effective in reducing the use of antibiotics in URTI cases.

Another strategy used to reduce the use of antibiotics is to delay the prescription of antibiotics. Different methods of delaying prescriptions (such as giving prescriptions with instructions, leaving prescriptions for collection, post-dating prescriptions, or requesting recontact) have been used [17]. With the strategy of delaying antibiotic prescriptions, less than 40% of patients are likely to use antibiotics [18, 19].

Clinical guidelines (CG) can be defined as "any document containing recommendations for clinical practice", that are systematically developed in order to assist decisions about appropriate health care for specific clinical circumstances [20, 21]. CG are used to reduce variability in practice when the scientific evidence is sparse or when multiple therapies are available. The development and implementation of evidence based CG is intended to organize and provide the best available evidence to support clinical decision-making in order to improve quality of care, patient outcomes, and cost-effectiveness [22]. CG have been shown to be effective tools to improve the appropriate use of antibiotics in hospital settings [23–25]. Taking into account the evidence published to date, researchers consider that the implementation of CG could reduce the prescription of antibiotics in URTI cases in primary care setting.

Materials and methods

Ethics approvals for the protocol and the study were granted by the Subcommittee for Research Ethics on Human Beings–PUCE with authorization code SB-CEISH-POS-93. The Ethics Committee established the non-need for informed consent for this study.

Study design and population

The aim of this quasi-experimental, before and after study, was to analyze the short- and long-term effects of the implementation of CG at a health care facility, and to decrease the rate of antibiotic prescription in URTI cases. The CG were implemented in the emergency department of a specialized private health care facility (third-level hospital) in Quito, Ecuador. The study's population consisted of patients from three moments in time, a baseline and two post-implementation cohorts. All of these consisted of patients registered in the hospital's health records (HR) with a primary diagnosis of URTI according to The International Classification of Disease (ICD) 10 codes, Table 1. The baseline was measured from January 1, 2010 through March 31, 2010. The implementation process of the CG was from May 1, 2010 through

Table 1. ICD-10 codes considered as URTI for the purpose of this study.

• J00 Acute nasopharyngitis [common cold] • J01 Acute sinusitis *(includes J01.0, J01.1, J01.2, J01.3, J01.4, J01.8, J01.9)* • J02 Acute pharyngitis *(includes J02.0, J02.8, J02.9)* • J03 Acute tonsillitis *(includes J03.0, J03.8, J03.9)* • J04 Acute laryngitis and tracheitis *(includes J04.0, J04.1, J04.2)* • J05 Acute obstructive laryngitis [croup] and epiglottitis • J06 Acute upper respiratory infections of multiple and unspecified sites *(includes J06.0, J06.8, J06.9)* • J10 Influenza due to other identified influenza virus *(includes J10.1)* • J11 Influenza due to unidentified influenza virus *(includes J11.1)*
Following codes also were considered as URTI, diseases of the middle ear categorized according to ICD-10 as:
• H65 Nonsuppurative otitis media • H66 Suppurative and unspecified otitis media

ICD: International Classification of Disease, URTI: Upper respiratory tract infection

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December 31, 2010. Post-implementation was measured from January 1, 2011 through March 31, 2011, and 7 years later, from January 1, 2018 through December 31, 2018.

Intervention

Researchers considered the intervention as the introduction process of the CG, which included different phases. The CG that were chosen for implementation, considering the lack of National CG for URTI cases in Ecuador, were the Clinical Guidelines CG69, "Respiratory Tract Infections (self-limiting): prescribing antibiotics" by the National Institute for Health and Care Excellence (NICE) [26]. The guidelines provide information on the diagnosis and treatment of URTI cases and offer prescription recommendations for antibiotics, such as for clinically compromised patients or patients with comorbidities, who are at high risk of bacterial superinfection. The CG propose practical strategies for prescribing antibiotics in children and adults, such as: 1. Immediate antibiotic prescription, 2. Delayed antibiotic prescription and 3. No antibiotic prescription. Table 2 describes the criteria for cases that need antibiotic prescription for each ICD-10 category, according to the NICE CG.

The implementation of the CG consisted in five different phases:

1. An explanation of the need for rational antibiotic prescription practices and guidance to the main stakeholders (hospital authorities and all clinicians that work in the emergency department) involved with antibiotic prescription problems at different hospital levels was

Table 2. Need for prescription of antibiotics in URTI according to the guideline using ICD-10 codes.

ICD-10 code	Criteria for Appropriate Antibiotic Prescription
H65 Nonsuppurative otitis media **H66** Suppurative and unspecified otitis media	**H65** must meet both conditions: presence of Acute Bilateral Otitis media AND age <2 **H65** or **H66** with presence of otorrhea
J01 Acute sinusitis	Must meet all conditions: Fever of >38C°, purulent discharge and facial pain
J02 Acute pharyngitis **J03** Acute tonsillitis	Must meet **3 of the following CENTOR criteria**: • Presence of tonsillar exudate • Presence of painful anterior cervical lymphadenopathy or lymphadenitis • Fever (>38°C) • Absence of cough
J00 Acute nasopharyngitis [common cold] **J01** Acute sinusitis **J02** Acute pharyngitis **J03** Acute tonsillitis **J04** Acute laryngitis and tracheitis **J05** Acute obstructive laryngitis [croup] and epiglottitis **J06** Acute upper respiratory infections of multiple and unspecified sites **J10** Influenza due to other identified influenza virus **J11** Influenza due to unidentified influenza virus	**Must meet any** of the following criteria: • Presence of one or more of the following comorbidities: Cardiac, Pulmonary, Renal, Hepatic, Neuromuscular, Immunosuppression, Cystic Fibrosis, Diabetes Mellitus. **OR** • Age <2 years old **AND** history of prematurity **OR** • Age >65 years old **AND** presence of cough **AND two or more** of the following: ▪ Hospitalized (recent) ▪ Diabetes mellitus ▪ History of cardiac arrest ▪ Current use of corticosteroids **OR** • Age >80 years old **AND** presence of cough **AND one or more** of the following: ▪ Hospitalized (recent) ▪ Diabetes mellitus ▪ History of cardiac arrest ▪ Current use of corticosteroids

URTI: Upper respiratory tract infection, ICD: International Classification of Disease, there are no ICD-10 codes for J07 and J08. J09 excluded because it refers to influenza

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carried out. The objective was to increase awareness about the adequate prescription of antibiotics in URTI cases and the possibility of reducing the use of antibiotics through the implementation of clinical guidelines. This was followed by the acceptance of the implementation by all physicians.

2. Diffusion of the guidelines by distribution of hard copies of the CG to all clinicians was performed. The copies were also sent via electronic mail, along with relevant background information that could help clinicians apply the CG.
3. An educational campaign was furtherly carried out by experts on the field: three family physicians and one infectious disease specialist, to improve knowledge of URTIs, focusing on improving the correct diagnosis and reducing the use of antibiotics. Posters with treatment algorithms were published in work areas of healthcare providers and nursing stations around the hospital. A total of five training sessions were provided in the implementation period. The training sessions lasted two hours and the teaching strategy was applied through educational games (like jeopardy games), leaflet distribution and pocket leaflets. Patient information sheets were also available for distribution; in this way, clinicians could provide the patients with URTI cases with general recommendations and align their prescriptions with the guideline recommendations.
4. Consistent feedback from the implementation team to physicians was also applied to reinforce proper management and treatment of URTI cases through individual audit sessions each week during the implementation period.
5. Guarantee of sustainability through continuous training was the last phase of implementation. The clinicians committed to continue the dissemination of the CG and the educational campaign every year to all clinical staff in the emergency department and whenever there would be a new staff member in the department.

Sample

The sample was defined as all the patients that met the inclusion criteria and that had complete information in their HR. A simple probabilistic type sampling was performed. The sample for the baseline and two implementation period cohorts consisted of patients with a main diagnosis of URTI according to ICD-10 codes in the emergency department. The following formula was applied to calculate the sample for a finite universe, $n = N^{*} Z^{2*} p^{*} q \,/\, d^{2*} (N\text{-}1) + Z^{2*} p^{*} q$, in each period of time.

In this formula, N represents population size, Z is the confidence level (95%), p is the probability of success, or expected proportion (50%), q is the probability of failure (50%), and d is precision (3% of maximum admissible error in terms of proportion). We decided to increase the sample by 10% considering possible losses. The subsequently studied sample comprised 114 HR for baseline, 114 HR for post-implementation cohort 2011 and 216 HR for post-implementation cohort 2018.

HR were selected according to the sample number among all cases of URTI registered in the emergency department. The selection of HR was randomized through a computer software that threw random numbers automatically (Epidat 4.1 version statistical software). None of the HR were excluded, as they had all the required information properly recorded.

Data source and data collection

In order to analyze the effect of the intervention in reducing antibiotic prescription, data from the HR from all the patients included in the three different cohorts mentioned was used. The collected data comprised the patient's age, sex, clinical presentation, and presence of comorbidities related to the criteria for prescribing antibiotics according to the CG, Table 2. A follow-up of the patients was performed until the moment of the clinical discharge of the URTI episode (including any visits of the patient to any other outpatient department). Complications were considered for this study as the need for hospitalization for any reason related to the primary diagnosis of URTI and the subsequent need for antibiotics during patient follow-up. Data were anonymously and manually extracted from the HR simultaneously by two peer reviewers, according to the following criteria:

- Inclusion criteria: Patients 3 months of age and above who required clinical ambulatory care for URTIs in the emergency department.
- Exclusion criteria: Patients whose primary diagnosis of URTI was determined by another outpatient department of the hospital.

After individual data extraction, the information was compared, and a consensus of inclusion or exclusion was reached for each patient. Two types of health professionals worked in the designated department and diagnosed the patients with URTI that were included in the study. These health professionals are classified as:

- Family Medicine Doctor: Medical specialist who has completed a 3-year postgraduate degree in general medicine.
- Emergency physician: Medical specialist who has completed a 3 to 4-year postgraduate degree in Emergency Medicine.

The need for antibiotic prescription was assessed according to the recommendations in the CG. The criteria for justified prescription of antibiotics are shown in Table 2. The HR were evaluated by two independent reviewers (medical specialists in primary care) and when there was inconsistency between the reviewers, this was resolved by consensus.

Antibiotic prescription evaluation

The antibiotic prescription rate was defined as the number of antibiotic prescriptions divided by all patients diagnosed with URTI, and appropriate prescription rate as the number of appropriate antibiotic prescriptions according to the NICE CG recommendations, divided by all patients receiving antibiotics.

Statistical analysis

The variables included in this study were both categorical and quantitative. The researchers performed a descriptive analysis with categorical variables through frequency distributions, proportions, and rates, and an analysis of quantitative variables through measures of central tendency and dispersion. The differences between the proportions of the variables in the cohorts (baseline, and post-implementation periods) were evaluated using the z test (*t-test* for independent proportions), where $p<0.05$ was considered significant. Epidat 4.1 version statistical software was used for data analysis.

Results

The general characteristics of the patients are described in Table 3.

The study included 444 patients with a main diagnosis of URTI that met the inclusion criteria. They were distributed in three groups: i) a baseline cohort (n = 114), ii) a first post-

Table 3. Characteristics of the sample.

Characteristic	Baseline 2011 n = 114	Post-implementation 2011 n = 114	p value	Post-implementation 2018 n = 216	p value
Age Mean (SD)	22.98 (21.07)	25.35 (20.42)	0.389	33.37 (28.05)	0.003
Gender					
Male	56 (49.12)	51 (44.73)	0.507	96 (44.44)	0.959
Female	58 (50.87)	63 (55.26)	0.507	120 (55.55)	0.959
Diagnosis					
Acute tonsillitis	23 (20.17)	4 (3.5)	<0.0001	19(8.79)	0.073
Acute pharyngitis	15 (13.15)	8 (7)	0.12	55 (25.46)	<0.0001
Acute nasopharyngitis	53 (47.49)	47 (41.2)	0.838	68 (31.48)	0.077
Acute laryngitis	13 (11.40)	14 (12.3)	0.838	1 (0.46)	<0.0001
Acute sinusitis	4 (3.50)	4 (3.50)	1	11 (5.09)	0.511
Acute bronchitis	3 (2.63)	5 (4.40)	0.472	36 (16.66)	0.001
Acute otitis media	2 (1.75)	6 (5.26)	0.150	8 (3.70)	0.504
Influenza	1 (0.87)	26 (22.80)	<0.0001	18 (8.33)	<0.0001
Comorbidity	4 (3.50)	3 (2.63)	0.701	4 (1.85)	0.640
Health professional					
Emergency	75 (65.78)	81 (71.050	0.393	139 (64.35)	0.219
Family Medicine	39 (34.21)	33 (28.94)	0.393	77 (35.64)	0.219

Data are presented as number (percentage) of patients except where noted, SD: Standard deviation

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implementation cohort 2011 (n = 114), and iii) a later post-implementation cohort 2018 (n = 216). Overall, patients in all three time periods had similar demographic characteristics.

Acute nasopharyngitis (common cold) was the most common diagnosis among the baseline and the post-implementation cohorts of 2011 and 2018, representing 47.4%, 41.2% and 31.48%, respectively. Amid the three periods, most of the diagnoses were made by emergency physicians: 65.8%, 71.1% and 64.35%, respectively.

There was a significant difference between the baseline and the post-implementation cohort of 2011 in the diagnosis of acute tonsillitis (20% vs 3.5%; $p<0.0001$), and in the diagnosis of influenza (0.87% vs 22.8%, $p<0.0001$). Differences between the post-implementation cohort of 2011 and the post-implementation cohort of 2018, were significative in the diagnosis of acute pharyngitis (7% vs 25.4%, $p<0.0001$), acute laryngitis (12.3% vs 0.46%, $p<0.0001$) and influenza (22.8% vs 5.09%, $p<0.0001$).

Antibiotic use

Broad spectrum antibiotics were used in all patients during the three periods, as shown in Table 4. Azithromycin and penicillin G benzathine were the most prescribed antibiotics in the baseline cohort (36.73% and 24.48%, respectively). Amoxicillin-clavulanate and penicillin G benzathine were the most prescribed antibiotics in the post-implementation cohort of 2011 (42.85% and 19.04%, respectively) and in the post-implementation cohort of 2018 (37.5% and 17.85%, respectively). There was a significant reduction in the use of azithromycin between the baseline period and the post-implementation cohort of 2011 (36.73 vs 9.52%, $p = 0.021$).

Antibiotic prescription rate and appropriate antibiotic prescription rate

Antibiotic prescription rates in the post-implementation cohort of 2011 were significantly reduced when compared with the prescription rates in the baseline. Antibiotic prescriptions decreased by 24.5% (42.9% in the baseline vs 18.4% in the post-implementation cohort of

Table 4. Antibiotic use.

Antibiotic	Baseline 2011	Post-Implementation 2011	*p* Value	Post-Implementation 2018	*p* Value
Azithromycin	18/49 (36.73)	2/21 (9.52)	0.021	9/56 (16.07)	0.465
Amoxicillin	2/49 (4.08)	2/21 (9.52)	0.369	6/56 (10.71)	0.879
Cefuroxime	6/49 (12.2)	2/21 (9.52)	0.743	4/56 (7.14)	0.728
Cephalexin	1/49 (2.04)	0/21 (0)	0.053	3/56 (5.35)	0.917
Clarithromycin	0/49 (0)	2/21 (9.52)	0.15	3/56 (5.35)	0.509
Penicillin G Benzathine	12/49 (24.48)	4/21 (19.04)	0.619	10/56 (17.85)	0.904
Amoxicillin clavulanate	10/49 (20.40)	9/21 (42.85)	0.053	21/56 (37.50)	0.668

Data are presented as number (percentage) except where noted

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2011, p<0.0001). There was not a significant difference in antibiotic prescription rates between the two post-implementation periods (18.4% vs 25.9%, p = 0.125), (Table 5). Appropriate antibiotic prescription rates between the baseline and the post-implementation cohort of 2011 were significantly increased by 44.2% (22.4% vs 66.6%, p<0.0001). There were no significant differences in appropriate antibiotic prescription rates between the two post-implementation periods (66.6% vs 50%, p = 0.191), as shown in Table 5.

Differences in antibiotic prescription rates in children and adults are shown in Table 6. There was a significant reduction of 31.6% (*p*<0.001) in the antibiotic prescription rate in the group of adults after the early implementation, but no differences were found in the children group. There were no differences between the two post-implementation periods.

Diagnosis-specific antibiotic prescription rates are shown in Table 7. After the early implementation, there was a reduction of 18.4% (p = 0.008) in antibiotic prescription rates when the diagnosis was acute nasopharyngitis, but there were no significant differences between the two post-implementation periods. For the rest of diagnoses, antibiotic prescription rates were similar among different periods. In the cases where there was a decrease in antibiotic prescription, there were not any medical complications reported during either of the three periods.

Discussion

The implementation of CG requires changes in the attitudes and behavior of health professionals as well as adaptations of the structural environment [27, 28]. We implemented CG in order

Table 5. Antibiotic prescription and appropriate antibiotic prescription.

Variable	Baseline 2011	Post-Implementation 2011	*p* Value	Post-Implementation 2018	*p* Value
Antibiotic prescription	49/114 (42.98)	21/114 (18.42)	<0.0001	56/216 (25.92)	0.125
Appropriate prescription	11/49 (22.44)	14/21 (66.66)	<0.0001	28/56 (50.00)	0.191

Data are presented as number (percentage) of patients except where noted.

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Table 6. Antibiotic prescription rates in children and adults.

Variable	Baseline 2011	Post-Implementation 2011	*p* Value	Post-Implementation 2018	*p* Value
Children	20/53 (37.73)	10/45 (22.22)	0.097	21/90 (23.33)	0.885
Adults	29/61 (47.54)	11/69 (15.94)	<0.001	35/126 (27.77)	0.063

Data are presented as number (percentage) of patients except where noted.

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Table 7. Diagnosis-specific antibiotic prescribing rates.

Diagnosis	Baseline 2011 n = 114	Post-implementation 2011 n = 114	p value	Post-implementation 2018 n = 216	p value
Acute tonsillitis	20/23 (86.95)	4/4 (100)	0.687	11/19 (57.89)	0.307
Acute pharyngitis	6/15 (40.00)	2/8 (25.00)	0.472	10/55 (18.18)	0.646
Acute nasopharyngitis	12/53 (22.64)	2/47 (4.25)	0.008	5/68 (7.35)	0.495
Acute laryngitis	4/13 (30.76)	3/14 (21.42)	0.580	1/1 (100)	0.347
Acute sinusitis	4/4 (100)	3/4 (75.00)	0.621	9/11 (81.81)	0.770
Acute bronchitis	1/3 (33.33)	4/5 (80.00)	0.187	14/36 (38.88)	0.083
Acute otitis media	2/2 (100)	2/6 (33.33)	0.343	4/8 (50.00)	0.533
Influenza	0/1 (0)	1/26 (3.84)	0.056	2/18 (11.11)	0.056

Data are presented as number (percentage) except where noted

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to reduce antibiotic prescription rates in a common group of related diseases treated in ambulatory settings.

The results of this study show an antibiotic prescription rate of 42.90% before the CG implementation. This number turned out to be even higher than the one obtained by our previous study in Ecuador from 2015, where the rate of prescription for antibiotics in URTI cases in an ambulatory care center was 37.5% [29]. Studies from all over the world have estimated an average of around 50% [30–37] of antibiotic prescriptions in URTI cases. Cordoba, et. al published a study in 2016 [38] involving four Latin-American countries; said study evaluated antibiotic prescription practices in URTI diagnoses in primary care health centers. The rates of antibiotic prescription were: 40% in Bolivia, 35% in Argentina, 27% in Uruguay, and 24% in Paraguay. In Mexico, Doubova et al. [39] reported more than 61% of antibiotic prescriptions in children diagnosed with non-streptococcal URTI after a first visit to the health facility. Even if these studies did not evaluate the appropriate prescription rate, the results are comparable to the current research.

An appropriate antibiotic prescription rate of 22.4% was found before CG implementation, reflecting an inappropriate prescription rate of almost 80%. A study done by Bagger et al. [8] in Argentina, Denmark, Lithuania, Russia, Spain, and Switzerland reported a 50% of inappropriate antibiotic prescription rates in URTI and almost 100% of inappropriate antibiotic prescriptions for common cold and otitis media. Holloway et al. [40] investigated the treatment of childhood infections in 78 lower-middle income countries between 1990 and 2009; after the review of 344 studies, the results showed a high percentage of URTI cases treated with antibiotics, with this percentage increasing over time (from 42% before 1990 up to 72% in 2006–2009). The study reports 25.8% of inappropriate antibiotic use in URTI cases for Latin America and 47.1% in lower-middle income countries in general. These studies show a comparable inappropriate antibiotic prescription rate in URTI cases to the one found in this paper.

Our results demonstrate that after the implementation of the CG, the prescription rate of antibiotics was significantly reduced by 24.6% in all patients. This result is similar to that reported in a study conducted in the United States [41], in which the strategy included CG implementation aimed to reduce the use of antimicrobials for the treatment of URTI cases in adult and pediatric patients in four primary care clinics. The intervention consisted of half-day educational sessions, delivery of CG, and case study presentations to review the appropriate URTI treatment and diagnosis. After the implementation, there was a significant reduction in the rate of antibiotic prescription by 24.6% in all physicians. In a study from Thailand [42] that determined the effectiveness of the implementation of CG in prescribing antibiotics for adults with URTI, there was a significant reduction of 29.9% in the antibiotic prescription rate. The results from this study are almost identical to ours (antibiotic prescription rate in adults reduced by 31.6%). The implementation strategies applied were educational interventions through two sessions of interactive educational meetings during a month and the distribution of a simple one-page clinical practice protocol. This study showed that strategies that involve educational campaigns, feedback of cases and educational material (e.g. clinical guidelines) in the implementation process are effective. Systematic reviews where physician-targeted multiple interventions or multifaceted interventions containing at least educational material proved effective in reducing antibiotic prescription rates in URTI cases [15, 43].

A significant reduction in the diagnosis of acute tonsillitis was found after early implementation. This result can be attributed to a better diagnosis in URTI cases made by physicians, as this is one of the objectives of the NICE guideline. Nevertheless, despite this reduction, the antibiotic prescription rate in acute tonsillitis remained high. On the other hand, the diagnosis of acute nasopharyngitis (common cold) was the same among different periods, but antibiotic prescription rate was significantly reduced for this condition.

Even though antibiotic prescription rates in children were reduced according to the results, this was not statistically significant. This could be because a low antibiotic prescription rate in children (37.7%) was found in our sample. International data report a global antibiotic prescription rate of 47.3% [44] in URTI cases in children; countries like Italy and Canada have higher rates (42% - 57%) and the Netherlands and the United Kingdom have lower rates (14% - 21%). We hypothesize that the implementation of CG to reduce the prescriptions of antibiotics in children would be effective in settings with higher rates of antibiotic prescription.

Implications for practice

CGs are relevant tools which should be implemented in order to reach better outcomes in health care. CGs are one important piece of the larger evidence-based practice actions needed to provide better health care. Despite all initiatives to develop such tools, their uptake in practice is not apparent. Developing good quality CGs does not ensure that the recommendations will be implemented in healthcare practice; therefore, the final effect in real practice is never guaranteed. As a matter of fact, the emphasis must shift from guideline development to strategy of implementation [45, 46]. Specific strategies designed to handle possible obstacles during implementation are needed to improve adherence to recommendations. A comprehensive strategy to disseminate the CG appears to be very important, followed by constant support in the learning process as well as a well-designed and well-prepared implementation process [47].

Limitations of the study

Some limitations can be identified in this study. The results are subjected to period effect, even though we analyzed three different time periods (one baseline and two post-implementation periods). A design that includes post-implementation analyses for each year would be more precise in measuring the change of patterns in antibiotic prescription practice. Additionally, the sample size of the baseline of the study was calculated a priori, but the defined time period was chosen based on the researcher's convenience, which could have led to selection bias. However, in any case, this limitation would in fact diminish the effect of CG implementation in the long term, but the results have been maintained. We believe that generalization of the results is limited because the implementation of the CG was carried out in a single private institution, although similar patterns in antibiotic prescription have been described in different scenarios [48].

Another limitation of this study is the lack of a National Clinical Guideline for URTIs, provoking a consideration for the use of an international guideline from a source that has been previously used by the Ministry of Public Health in Ecuador. A further limitation that can be mentioned is the lack of adoption of a delayed prescription strategy by physicians which should be included in the CG. This can be explained because of the context in an emergency department as compared to that of an outpatient clinic, making it complicated for patients to request recontact or for physicians to leave prescriptions for later collection; however, patient follow up was performed on the patients and there was no subsequent need for antibiotics in the post-implementation periods.

Strengths of the study

The strength of the study is found within the methodology for the implementation process. Different levels were included to make a proper implementation process. The success of the CG implementation depended on the consideration of different barriers (related to physician factors, guideline related factors, and external factors) and the use of appropriate strategies to overcome them [20]. The participation of all clinical staff and stakeholders in management was necessary in order to generate awareness and commitment at the provider level as well as support at the administrative level. The dissemination of the CG was extensive and key recommendations were also provided to promote familiarity with the information, generating positive expectations about the plausibility of the recommendations. In addition, the study provided accompaniment in the learning process through educational campaigns, with future reinforcement of what had been learned and positive individualized feedback during training and in practice. We believe that all of these strategies were properly implemented and prompted the success of our intervention.

Implications for future research

Given the success of the implementation of the CG to reduce unnecessary antibiotic prescription in URTI cases in the study, the proposed intervention might be applicable for other common diseases in which prescription is necessary to improve the health of the patient. Considering that the implementation of a CG does not require a significant time commitment or significant financial resources, future studies could be carried out to identify the real effect of this strategy to improve prescription practices.

Conclusions

Implementation of CG to reduce unnecessary antibiotic prescription on self-limited URTI cases was effective. The results are remarkable after the early implementation, but the effect can only persist during time as long as the strategy of implementation not only includes aspects related to the guideline but also aspects related to stakeholders, medical staff, and accompaniment in the learning process.

Supporting information

S1 Data.
(XLSX)

S2 Data.
(XLSX)

Author Contributions

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Capítulo IV. Consideraciones Finales

4.1 Discusión

Los resultados de esta investigación revelan que existe una proporción de prescripción antibiótica en IRAs en el primer nivel de atención de salud en Ecuador del 37.5%. Este valor se encuentra por debajo de la proporción estimada en países ingresos económicos medios y altos del 50%[53,54]; pero similar a países de la región de América Latina, como es el caso del 35% en Argentina, 40% en Bolivia, 24% en Paraguay, 27% en Uruguay y del 61% en México[55,56]. No obstante, es importante mencionar que la necesidad real de prescripción antibiótica, considerada como la cantidad de pacientes que requerían un antibiótico, fue de solo el 3.7% en este estudio.

Esta investigación demostró que tan solo en 9.75% de los pacientes recibió una prescripción adecuada de antibióticos en IRAs. Esto refleja un 90.25% de prescripción inapropiada en IRAs en el primer nivel de atención en salud en Ecuador, siendo un dato muy superior al reportado para la región de América Latina del 25.8%[38].

Es importante mencionar que para esta investigación se tomó como referencia una GPC para determinar la prescripción inapropiada de antibióticos, teniendo en consideración que por cada uno de los posibles diagnósticos de IRAs según CIE-10, existen ciertos criterios que justifican la prescripción antibiótica; por ejemplo, la edad, la presencia de comorbilidades y algunos síntomas que pueden denotar gravedad en un paciente (Tabla 1). Esto permitió determinar que en los pacientes que cumplieron criterios para una prescripción de antibióticos, no los recibieron en un 35.2% de los casos. El uso inapropiado de antibióticos se extiende no solo al hecho de la sobre prescripción antibiótica, si no de la no prescripción cuando esta es necesaria.

En Ecuador el médico general es el tipo de médico más común en atención primaria; sin embargo, la atención por médicos familiares y médicos pediatras cuenta para un gran número de casos. El análisis de esta investigación mostró que la proporción de prescripción antibiótica en IRAs es menor en los médicos familiares y pediatras, en comparación con médicos generales. Una explicación a esta situación puede deberse al mayor grado de especialización y mayor tiempo de formación profesional.

La atención de IRAs representa un importante consumo de recursos sanitarios y por tanto genera un gasto sanitario considerable. Los resultados de esta investigación revelaron que las atenciones médicas iniciales y las consultas de seguimiento representaron el 20.44% de todo el consumo de recursos sanitarios directos en la atención en el primer nivel en IRAs en niños. La proporción de consultas de seguimiento fue del 22%, teniendo en consideración que estas infecciones son autolimitadas; sin embargo, esta proporción es similar a la reportada a nivel internacional[57,58]. Las causas de consulta de seguimiento pueden deberse a consultas de revaloración, presencia de complicaciones, resolución tardía de los síntomas, presencia de nuevos síntomas o diagnóstico incorrecto; no obstante, en esta investigación todas las consultas de seguimiento fueron por revaloración del paciente.

La prescripción de medicamentos es el recurso sanitario más consumido en la atención de IRAs. Esta investigación determinó que los medicamentos cuentan por el 74.1% de todos los recursos utilizados en la atención; esto se debe a que la proporción de prescripción de medicamentos fue del 95.52%, dato superior a lo reportado en países desarrollados, donde esta proporción se ubica entre el 51% y 70%[59]. La proporción de prescripción antibiótica en el estudio de consumo de recursos fue del 45.26%, superior a lo que evidenciamos anteriormente, el cual fue de 36.9% en niños con IRAs. Por otro lado, el uso de exámenes complementarios para el diagnóstico de IRAs fue menor al 5%, en concordancia al hecho de que generalmente no se requieren exámenes para el abordaje de estas enfermedades según lo reportado en la literatura[60].

El alto consumo de recursos sanitarios en la atención IRAs se traduce a un costo importante. El costo medico directo de un solo episodio en IRAs en niños en el primer nivel de atención de salud en Ecuador fue estimado de I$ 37.28 (I$ 2017 dólares internacionales). Al clasificar los costos por su naturaleza, se estimó que el costo de la atención directa del profesional sanitario fue de I$ 26.76, es decir el 72% de todo el costo sanitario por episodio. Además, es importante mencionar que el costo de una consulta de seguimiento fue de I$ 19.23, lo que significa que el costo en dichos casos se incrementa en un 71%; este dato es de importancia, ya que la conducta de revaloración incrementa los costos sanitarios significativamente, teniendo en cuenta que este tipo de infecciones son autolimitadas y que el riesgo de complicaciones es bajo. Por otro lado, la prescripción de medicamentos representó el 14%

de todo el costo por episodio de IRA, de este valor, el 58.94% corresponde al costo de prescripción de antibióticos.

Estos datos permitieron estimar el costo anual por atención en IRAs en niños en el primer nivel de atención en el año 2017 para el MSP, que fue de alrededor de I$ 50.4 millones. Sin embargo, si la proporción de prescripción antibiótica hubiera sido 50% más baja, se hubiera realizado un ahorro de I$ 2.3 millones. En adición, el costo por uso de otras medicinas no recomendadas para el manejo de IRAs (ej. antitusígenos, mucolíticos y antihistamínicos) también representa un alto coste, y podría reducir el costo total al SNS a I$ 46.65 millones. Por lo anterior mencionado, establecer cuáles son los factores que promueven esta conducta de prescripción e identificar estrategias de intervención encaminadas al uso racional de medicamentos podría contener costos sanitarios.

La prescripción antibiótica en IRAs se encuentra influenciada por factores intrínsecos y extrínsecos relacionados al prescriptor. Este estudio evaluó los factores intrínsecos como el género, residencia, lugar de práctica clínica, experiencia clínica y la exposición a educación médica continua y cómo influyen en los CAP de los prescriptores. Los resultados demostraron que los conocimientos respecto a la prescripción antibiótica en IRAs son limitados, menos de la mitad de los médicos evaluados alcanzaron un score aceptable respecto a tópicos de etiología, diagnóstico y tratamiento, teniendo en cuenta que es una de las patologías a las cuales más frecuentemente se enfrentan en su práctica clínica. Estos resultados son similares a los reportados en la literatura científica respecto a los conocimientos de los médicos sobre la prescripción antibiótica[61,62]. Los factores intrínsecos que denotaron un menor nivel de conocimiento fueron la región geográfica de la Costa y el género femenino; estos resultados son contrarios a los publicados en otros contextos[63]. Es posible que la influencia de estos factores en la población ecuatoriana se deba posiblemente a aspectos socioculturales. Estos resultados reafirman que los factores intrínsecos en la educación médica deben ser explorados desde una visión local y socio-cultural[64,65].

A pesar de que la evaluación de resultados respecto a los conocimientos en prescripción antibiótica en IRAs fue deficiente, las actitudes y prácticas hacia una prescripción racional de antibióticos fueron positivos. Los médicos mostraron una actitud positiva a la adopción de estrategias que mejoren el uso racional antibióticos, mediante la no prescripción de antibióticos o una prescripción tardía de los mismos. Esto representa una importante oportunidad para establecer intervenciones que estimulen el uso racional de antibióticos en IRAs.

El desarrollo de habilidades de prescripción a través de educación médica continua y programas de postgrado podrían mejorar los CAP en IRAs. Esta investigación pudo determinar que un programa de postgrado en atención primaria (medicina de familia), mejora los niveles de CAP en los médicos, las relaciones de proporción de mejores conocimientos y prácticas en IRAs fueron mayores en aquellos estudiantes de la segunda mitad del programa de especialización en medicina familiar comparados con los de la primera mitad del programa. Esto puede explicarse debido a que los médicos recién graduados y no especializados tienen menos oportunidades de exposición y preparación para la práctica clínica[66]. Por otro lado, los modelos de enseñanza médica basados en el modelaje profesional permiten el aprendizaje de altos estándares de competencia clínica[67]. Un programa de especialización en atención primaria como es medicina familiar incrementa las oportunidades de desarrollo de habilidades en prescripción de medicamentos en entornos controlados y supervisados.

El uso racional de medicamentos requiere cambios en las actitudes y el comportamiento de los profesionales de la salud, así como adaptaciones del entorno estructural; para ello, existen varias intervenciones. Las intervenciones más estudiadas para reducir la prescripción antibiótica en IRAs son: materiales educativos, auditoría y retroalimentación, sesiones educativas, cambios en los sistemas financieros y sanitarios, recordatorios y sistemas de asistencia electrónica, o intervenciones que incluyen varias de estas estrategias, conocidas como intervenciones multifacéticas[68]. Esta investigación logro determinar el efecto de una intervención multifacética a través de la implementación de una GPC en un escenario ambulatorio; se logró una reducción significativa de cerca del 25% de la proporción de prescripción antibiótica en IRAs, a corto plazo. En adición, la intervención mejoró la prescripción apropiada de antibióticos en un 44.2% y mejoró los tipos de diagnósticos relacionados a IRAs. Los resultados obtenidos en esta investigación concuerdan con estudios similares[52,69,70]; por otro lado, los efectos de la implementación a largo plazo se mantuvieron y no existieron diferencias significativas, lo que demuestra que una intervención multifacética puede mejorar el uso racional de antibióticos en IRAs. Teniendo en cuenta que la implementación de un GPC no requiere un compromiso de tiempo o recursos financieros significativos, se puede inferir que es una intervención efectiva para mejorar las prácticas de prescripción antibiótica en IRAs.

4.2 Conclusión

El uso inapropiado de antibióticos en patologías atendidas en el primer nivel de atención en salud es un problema de salud pública para el Ecuador. Las IRAs representan una importante carga de morbilidad ambulatoria en la cual se evidencia un uso no racional de medicamentos, especialmente antibióticos, lo cual incrementa significativamente el gasto sanitario. Las intervenciones multifacéticas que incluyen estrategias de educación en los prescriptores son herramientas muy efectivas en cambiar el comportamiento y las prácticas de prescripción antibiótica, mejorando el uso eficiente de recursos sanitarios y la calidad de la atención médica.

4.3 Recomendaciones

- Establecer estrategias multifacéticas para reducir el uso de antibióticos en IRAs permitirá disminuir el elevado consumo de recursos y gastos sanitarios para el Sistema Nacional de Salud del Ecuador.
- Es necesario explorar los factores extrínsecos del prescriptor relacionados al uso de antibióticos en el primer nivel de atención en salud en el Ecuador para identificar puntos críticos en los cuales intervenir con el objetivo de mejorar el uso racional de antibióticos.
- Establecer recursos de educación continua en médicos de atención primaria en salud permitirá el desarrollo de mejores habilidades de prescripción antibiótica en infecciones del tracto respiratorio superior.
- Investigar sobre prácticas de prescripción de medicamentos, especialmente de antibióticos, en otras patologías con mayor carga de morbilidad ambulatoria, con el fin de establecer líneas de base de la problemática del uso inapropiado de medicamentos en el primer nivel de atención en salud en el Ecuador y replicar intervenciones orientadas al uso racional de medicamentos.

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