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ORIGINAL PAPER

Estimating cost savings from reducing antibiotic overprescription in european general practices

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Abstract

Background Antibiotic (ATB) overprescription leads to antimicrobial resistance (AMR) and adverse events (AEs) and poses significant economic burdens on European healthcare systems. The aim of this study was to assess the economic impact associated with interventions aimed at reducing unnecessary ATB prescriptions in general practice, and to extrapolate the results at the European Union (EU) level.

Methods We used data from the "HAPPY PATIENT" project, a before-and-after study that implemented a multifaceted intervention in primary care settings in France, Greece, Lithuania, Poland, and Spain. Based on the outcomes observed in general practice across these five countries we extrapolated the results to estimate for each of the 27 EU member states: i) the costs of implementing the interventions, ii) the number of potentially unnecessary ATB prescriptions avoided, and iii) the potential savings due to reductions in unnecessary ATB prescriptions. We considered a realistic and an optimistic scenario: using the mean and the largest reduction in unnecessary ATB prescriptions observed across each of the five participating countries, respectively.

Results Across the EU, €2.7 billion are estimated to be spent annually on healthcare resources linked to potentially unnecessary ATB prescribed in general practice. Implementing the interventions across the EU is projected to cost €107 million. Positive net savings were estimated in both scenarios, €151 million in the realistic scenario and €423 million in the optimistic scenario. Several sensitivity analyses were conducted to characterise the substantial uncertainty surrounding these estimates, which yielded considerable potential savings in all cases.

Keywords Antibiotics · Prescriptions · Overuse · Antimicrobial resistance · Costs · Cost savings

JEL classification I11 · I18

Introduction

Inappropriate use of antibiotics (ATB) plays a crucial role in driving antimicrobial resistance (AMR) and leads to preventable ATBs-related adverse events (AEs). Research consistently shows that these AEs contribute to a substantial number of emergency department visits each year [1–7], placing a significant burden on healthcare systems worldwide. Furthermore, AMR, which is largely driven by excessive ATB use, is associated with devastating health and

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economic impacts. According to a meta-analysis, patients with resistant infections are estimated to have an 84.4% higher chance of dying compared to patients with a susceptible infection [8]. The same study also identified that the attributable excess cost of resistant infections was in the range of US$2,371 to US$29,289 per patient episode. The number of global deaths in 2021 attributable to and associated with AMR was estimated at 1.14 and 4.71 million, respectively [9]. Deaths are expected to increase steadily in the coming decades, yielding 1.91 million deaths attributable to AMR and 8.22 million deaths associated with AMR in 2050 [9]. According to the World Bank, drug-resistant infections could cause economic damage comparable to—or even worse than—the 2008 financial crisis. By 2050, annual global Gross Domestic Product (GDP) could decrease by 1.1% in a low-impact AMR scenario and by 3.8% in a high-impact scenario [10].

Given these data, reducing unnecessary ATB prescriptions is crucial for mitigating health-related impacts, reducing financial healthcare costs, and addressing broader economic losses. In response to this challenge, the European Union (EU) issued guidelines in 2017 promoting the prudent use of ATBs [11]. These guidelines, which are aimed at a wide range of stakeholders, including governments, healthcare professionals (HCPs) and patients, seek to curb overprescription and address the root causes of AMR.

The HAPPY PATIENT project (Health Alliance for Prudent Prescription and Yield of Antibiotics in a Patient-Centred Perspective) [12, 13] funded by the European Commission, aimed to put EU guidelines into practice by implementing a multifaceted intervention to reduce ATB overprescription in common infections such as respiratory and urinary tract infections. Conducted across five European countries—Spain, France, Poland, Lithuania, and Greece—the project focused on key HCPs in general practice, out-of-hours services, nursing homes, and community pharmacies.

The results of the HAPPY PATIENT project demonstrated a significant reduction in unnecessary ATB prescriptions in general practice settings [12]. Thus, using data from the five participating countries, this study analysed the potential cost savings of reducing unnecessary ATB prescriptions in general practice settings across Europe. To do so, estimates were scaled up to project the potential savings if such interventions were implemented across the EU. To characterise the substantial uncertainty surrounding these estimates, several sensitivity analyses were performed for critical model parameters and assumptions included in our calculations. Additionally, we provide a roadmap for scaling up these interventions across the EU, outlining the necessary conditions to ensure a successful implementation that could yield the expected results.

Methodology

Study setting and design

To estimate potential healthcare savings from reducing unnecessary ATB prescriptions we relied on data from the HAPPY PATIENT project, focusing on the impact observed in general practice as the multifaceted intervention in this setting demonstrated significant results [12]. The HAPPY PATIENT project is a before-and-after study which collected data during two audits following the Audit Project Odense (APO) methodology [13]. The first audit took place from February to April 2022, and the second from February to April 2023. During each audit, HCPs in general practices were instructed to record all consecutive patient contacts involving suspected infections in a simple reporting template, the APO chart, designed specifically for this project (see Supplementary online material 1).

Prior to the second audit, general practitioners (GPs) participated in a multifaceted intervention, on-line or face to face, that included: individual prescriber feedback on the first audit results at both the individual and group levels; a workshop with peer feedback and knowledge exchange to set quality improvement goals; a workshop on enhancing communication skills for consultations with patients with suspected community-acquired infections; and an introduction of the communication tools prepared by the HAPPY PATIENT team, including educational materials on ATB use, brochures, and handouts explaining the concept of the ATB footprint. An e-learning platform was also available for case discussions, focusing on appropriate ATB use for common infections, natural infection courses, and updated clinical guidelines for diagnosis and management. More detailed information on the study design and the interventions can be found in the study protocol [14].

Measuring potential cost savings of reducing ATB overuse

Estimating the net savings associated with reducing unnecessary ATB prescriptions involved three steps. First, we measured the cost per GP of implementing the interventions, secondly, we estimated the mean savings per unnecessary ATB prescription avoided, and thirdly, we scaled up these results to each European country and projected the expected intervention costs and the potential reduction in unnecessary ATB if the interventions were implemented at the country level across the EU. For the latter, two scenarios were considered: a realistic scenario using the mean reduction observed across the five participating countries, and an optimistic scenario using the largest reduction observed in one of the five participating countries in unnecessary ATB prescriptions [12]. Estimated savings for each country were calculated based on these projections for both the optimistic and realistic scenarios. We now provide further details for each of the steps undertaken for this analysis.

Step 1 – Estimating the cost of the intervention per GP

The cost of the interventions per GP was estimated considering that the interventions were addressed to all GPs in a given country. This was to provide a more realistic estimation of what would be the cost of the interventions developed in HAPPY PATIENT if they were implemented in real practice.

As mentioned above, the multifaceted interventions included face-to-face and/or online meetings and workshops, as well as the development and presentations of a series of communication tools and an e-learning platform. To estimate the cost of the multifaceted interventions per GP, three types of costs were defined:

i. Upfront (fixed) costs – refer to the costs of developing/adapting the interventions, regardless of the number of participants or meetings conducted. This includes, for example, the cost of developing, adapting and translating the communication tools and the cost of the time invested in uploading materials into the e-learning platform. In order to allocate these costs to an intervention cost per GP we divided them by the estimated total number of GPs hypothetically participating in the interventions if they were implemented at the country-level (more details below).
ii. Variable costs per group – refer to the costs of delivering the interventions to groups of professionals, considering a specific maximum number of participants per group. These costs, therefore, depend on the size of the groups of professionals participating in the interventions. Examples of this type of costs are the costs associated with the time spent by experts delivering the interventions to groups of GPs or the costs of printing materials that were presented at the intervention meetings. To calculate the cost per GP associated with this type of cost, we considered an average group size of 75 GPs for the organised meetings and an average of 30 GPs for the workshops.
iii. Variable costs per GP – refer to the costs directly related to the activity of the GPs, for example, their time spent in filling in the APO chart and cost of their time required to attend the interventions.

For each country, the costs of each cost component were obtained from the relevant HAPPY PATIENT teams or by surveying the persons responsible for implementing the interventions in each TC (i.e., country coordinators). When the costs provided by the TCs contained missing data, values were imputed considering the average values of the countries with available data.

Step 2 – Estimating the cost per ATB prescription

The cost per ATB prescription included three elements: the drug cost of the ATB, the cost of adverse events associated with the consumption of ATB, and the cost associated with AMR. Each of these components were measure as follows.

i. Drug costs per ATB prescription - To measure the costs associated with ATB consumption we calculated the cost per recommended daily dose (RDD) considering the unit drug cost per RDD and the usual daily dose of each ATB included on the APO chart. In the APO chart, ATBs were categorised by drug or class consisting of amoxicillin; amoxicillin-clavulanic acid; cephalosporins; fosfomycin; macrolides or clindamycin; nitrofurantoin; penicillins V or pivmecillinam; quinolones; tetracyclines; trimethoprim (andsulphonamides); and other ATBs (see Supplementary online material 1). Country-specific drug unit costs were obtained from the official websites of each country (France,[1] Greece,[2] Lithuania,[3] Poland,[4] and Spain[5]). While data for France, Poland, Greece and Spain represented regulated reimbursed prices, in Lithuania reimbursement prices were not publicly accessible, and so we used regulated maximum retail prices or, when these were unavailable, pharmacy retail prices. For each ATB class, we then estimated an average cost considering the average of all the ATBs included in the respective class (in sensitivity analysis we used the minimum and maximum drug costs). Then, for each patient, we multiplied the cost of the RDD of the prescribed ATB by the number of days of the duration of treatment recorded in the APO chart to obtain the medication cost per course of treatment.

[1] Data extracted from the France government website at 04/05/2023. Available from: https://sante.gouv.fr/soins−et−maladies/medicaments/; https://base−donnees−publique.medicaments.gouv.fr/

[2] Data extracted from the Greece government website at 24/02/2023. Available from: https://www.galinos.gr/web/drugs/main/atccodes/J01CE02.

[3] Data extracted from the Lithuania official website on medication at 23/02/2023. Available from: https://vaistai.lt; https://www.e−tar.lt/portal/lt/legalAct/28141980a31511ed8df094f359a60216.

[4] Data extracted from the Empendium Poland website at 08/03/2023. Available from: https://www.mp.pl/empendium/

[5] Data extracted from the Spanish government website at 30/11/2022. Available from: https://www.sanidad.gob.es/profesionales/nomenclator.do.; https://cima.aemps.es/cima/publico/home.html.

ii. Adverse event costs per ATB prescription – We estimated the costs of potential AEs associated with ATB use for each ATB class recorded in the APO chart. The probability of suffering an AE by ATB class was taken from Shehab et al. [7], who estimated and compared the rates of emergency visits for systemic AEs by drug class, individual drug, and event type. In this study, the authors estimated the annual number of emergency department visits per 10,000 outpatient prescription visits. The same probabilities for AEs by drug class were applied to ATB prescriptions in each of the five TCs (in sensitivity analysis, we applied the lower and upper bounds of the corresponding probabilities). Then, country-specific unit costs data for health care visits were collected for each TC: for inpatient bed day by hospital level (hospitalisation cost) and for outpatient visits (as a proxy for the cost of an emergency visit) from a publication by the World Health Organization (WHO) [15]. These values were updated to 2022 using the consumer price index (CPI) in each TC[6] and converted to euros, where appropriate, using the respective conversion rate.[7] When available, these costs were compared with more recent figures of country-specific unit costs and were judged by country coordinators to reflect current cost estimates. In addition, in the sensitivity analysis we used the minimum and maximum values reported in the WHO publication, which correspond to cost estimates for different hospital levels (primary, secondary, and tertiary).

Then, the mean cost of AEs per ATB prescription was estimated by multiplying the probability of an AE (specific to each ATB class) by the associated treatment cost, using Equation 1. This treatment cost is composed of two main components: the cost of an emergency department visit and the cost of a potential hospitalisation. The hospitalisation cost was calculated by considering the cost per inpatient day, the average length of stay (assumed to be 3 days for an AE-related hospitalisation [16]), and the probability that an AE led to hospitalisation (assumed at 6.1% based on Shehab et al. [7]). Using Eq. 1, each ATB prescription recorded in the APO registrations was assigned an estimated AE cost, which varied according to the drug class prescribed to each patient.

$$Cost_{AE} = Prob_{AE} * (Cost_{EV} + (Prob_{Hos} * Cost_{IP} * LOS)) \qquad (1)$$

where:

- $Cost_{AE}$ is the estimated cost of AEs per ATB prescription by country,
- $Prob_{AE}$ is the probability of an AE by ATB class,
- $Cost_{EV}$ is the cost of an emergency visit by country,
- $Prob_{Hos}$ is the probability that the AE leads to a hospitalisation,
- $Cost_{IP}$ is the cost per inpatient day by country,
- LOS is the length of stay of an AE-related hospitalisation.

iii. AMR cost per ATB prescription - To calculate the cost of AMR per ATB prescription, we applied the formula proposed by Shrestha et al. [17] (see Eq. 2). In their study, the authors estimated the economic burden of AMR by utilising an equation that incorporates three key components: the resistance modulating factor (RMf), which represents the correlation between human ATB consumption and the subsequent development of resistance; the economic costs of AMR for five major pathogens, including both direct and indirect treatment costs for all resistant strains; and the annual consumption of all ATB classes contributing to resistance in these pathogens.

$$cAMR_d = \sum \frac{Pp * (DCp + ICp)}{Q} \qquad (2)$$

where:

- $cAMR_d$ is the cost of AMR per standard unit of all ATBs consumed,
- $DCp + ICp$ are the direct and indirect cost of treatment for all resistant pathogens,
- Pp is the Resistance Modulating factor (RMf) Spearman's correlation coefficient showing ecological associations between average consumption and corresponding resistance,
- Q is the annual consumption of all ATBs.

We replicated this approach by collecting information on i) the RMf among European countries, ii) the annual direct costs due to AMR in each of the five TCs, and iii) the annual ATB consumption in each of the five TCs. Indirect costs were not considered due to the lack of data. To obtain the RMf, we used the correlation coefficients between human ATB consumption and subsequent resistance obtained in a study that investigated outpatient ATB use in 26 European countries [18]. From that study, the average of the Spearman's correlation coefficients recorded for all combinations of ATB was calculated and used as the RMf for each of the five TCs. Then, for each TC, we collected data on the estimated average annual healthcare expenditure associated with AMR using

[6] Consumer price index (CPI)Available from: https://www.worldbank.org/en/research/brief/inflation–database.

[7] Currency converter 2022. Available from: https://commission.europa.eu/funding–tenders/procedures–guidelines–tenders/information–contractors–and–beneficiaries/exchange–rate–inforeuro_pt.

figures estimated and published by the OECD [19]. When required, the amounts were converted to euros and inflated to 2022 prices using the Consumer Price Index (CPI) for each TC. Finally, to calculate the annual ATB consumption in each TC, we used data on the rate of community consumption of antibacterials for systemic use, expressed in Defined Daily Doses (DDD), as published by the European Surveillance of Antimicrobial Consumption Network of the European Centre for Disease Prevention and Control (ECDC) [20].

The mean AMR cost per ATB prescription was estimated by multiplying the average annual healthcare expenditure associated with AMR for each country by the RMf and dividing it by the annual consumption of ATB per year in each country (Equation 3). Because the information on ATB consumption published by the ECDC is expressed as DDD, the calculations defined above estimate the AMR cost associated with each DDD. To transform these estimates into the AMR cost per course of ATB prescription we multiplied this result by the ATB treatment duration recorded in the APO chart for each ATB prescription, which was estimated in 7.4 days.

$$Cost_{AMR} = \frac{TotalAnnualCost_{AMR} * RMf}{TotalAnnualConsumption_{ATB}} \times TTO_{Duration} \quad (3)$$

where:

- $Cost_{AMR}$ is the estimated cost due to AMR per ATB prescription by country,
- $TotalAnnualCost_{AMR}$ is the annual healthcare expenditure associated with AMR by country,
- RMf is the Resistance modulating factor,
- $TotalAnnualConsumption_{ATB}$ is the annual ATB consumption per year by country,
- $TTO_{Duration}$ is the average ATB treatment duration in days.

Step 3 – Upscaling potential saving at the EU level

After estimating the mean cost of the interventions per GP and the mean cost of ATB prescription in the five countries participating in the HAPPY PATIENT project, we extrapolated the results to estimate at the country-level for each of the 27 EU member states[8]: i) the costs of implementing the interventions, ii) the number of potentially unnecessary ATB prescriptions avoided, and iii) the potential savings due to reductions in unnecessary prescriptions.

In order to estimate the cost of implementing the HAPPY PATIENT intervention at the country-level we considered the total number of GPs in each country, which was taken from the OECD Health Statistics reports [21]. This source provides information on the number of all practising doctors and the percentage of GPs in each country. Data for Spain was missing from the OECD report, and instead, a report by the Spanish Ministry of Health was used. In the base case analysis, we assumed that 74% of GPs would participate in the interventions in each country, reflecting the participation rate observed in the HAPPY PATIENT interventions. In the sensitivity analyses, we varied this participation rate between 60 and 80%, in line with the range reported in other antibiotic stewardship interventions involving GPs [22, 23]. The average intervention cost per GP calculated for the five TCs was applied for countries not participating in the HAPPY PATIENT project.

To estimate the cost per ATB prescription in each EU country, information on the unit costs of healthcare services [15] and healthcare costs associated with AMR [20] were collected for each specific country. However, drug unit costs were not available for each of the 27 EU countries, and therefore, the mean unit cost of medication was applied across the five TCs to the remaining EU states. Treatment duration was also taken as the mean value across the five TCs for the remaining EU states.

Finally, to estimate the number of potentially unnecessary ATB prescriptions that could be avoided if HAPPY PATIENT interventions were implemented at the country level in each of the 27-member states, we considered the following steps. First, the number of ATBs prescribed by GPs annually was estimated in each country using country-specific data on the rate of the community consumption of antibacterials for systemic use published by the European Centre for Disease Prevention and Control [20]. The information on ATB consumption is expressed as DDD per 1,000 people per day, therefore, we multiplied this figure by the overall country-specific population and by 365 days and then divided by 1,000, to obtain the total annual consumption in DDD. Also, to estimate the number of ATB treatments prescribed (instead of DDDs consumed each year) the result was divided by treatment duration. In addition, we assumed that 96.4% of ATBs prescribed in the community are prescribed by GPs [24]. The formula used is summarised below (Eq. 4):

$$TotAnnual\_GP\_Presc_{ATB} = \frac{Prop_{GP} * \left[\frac{DDD*Pop*365}{1{,}000}\right]}{TTO_{duration}} \quad (4)$$

where:

- $TotAnnual\_GP\_Presc_{ATB}$ is the total annual ATB prescriptions made by GPs by country,
- $Prop_{GP}$ is the proportion of ATBs consumed at the community that are prescribed by GPs,

[8] Information for Cyprus and Malta was unavailable, so these two countries were excluded from the upscaling analysis.

- DDD is community consumption of ATB expressed as DDD per 1,000 people per day by country,
- Pop is the total population by country,
- $TTO_{duration}$ is the ATB treatment duration in days.

We then estimated the annual number of potential unnecessary prescriptions in each country, by applying the mean probability that was observed in the first APO registration conducted in general practices in HAPPY PATIENT across the five TCs. The percentage of potentially unnecessary ATB prescriptions in general practices in the first APO audit was estimated at 72.2% [12]. This was based on several algorithms defined according to the data collected on the APO chart on diagnoses, symptoms and duration, and tests conducted (see Supplementary online material 2). The last step involved estimating the expected reduction in unnecessary prescriptions achieved if HAPPY PATIENT interventions were applied in general practices in each country. For this, two scenarios were considered:

i. Realistic scenario: It uses the mean effectiveness estimated in general practices across the five TCs. This involves applying a 9.7% reduction to potentially unnecessary prescriptions in each country [12].
ii. Optimistic scenario: It uses the best result observed across the five TCs. This involves applying a 19.9% reduction (as observed in Lithuania) in potentially unnecessary prescriptions in each country [12].

In both cases, we assume that the effect of the intervention would last for a 12-month period (sensitivity analyses were performed using different assumptions about the duration of the effect). Potential savings were then measured by multiplying the number of expected potentially unnecessary ATB prescriptions avoided in each country by the mean cost per ATB prescription. To estimate the net savings, we then subtract the estimated costs of implementing the HAPPY PATIENT interventions from the estimated savings.

In addition to the base case analyses for the optimistic and realistic impact scenarios, we conducted four sensitivity analyses. In the first sensitivity analysis, we simultaneously varied three parameters: drug costs, probabilities of adverse events, and healthcare utilization costs. Drug costs were varied by applying the minimum and maximum unit cost values for each drug within each class. Adverse event probabilities were varied using the lower and upper bounds of the confidence intervals reported in the literature, and healthcare utilization costs (inpatient days and outpatient visits) were varied using the minimum and maximum values included into the WHO publication. The more conservative scenario (sensitivity analysis 1A) applies the minimum values for all three parameters, while the less conservative scenario (sensitivity analysis 1B) applies their respective maximum values. In the second sensitivity analysis, we varied GP participation rates between 60 and 80% (compared with 74% in the base case). To ensure consistency, we also adjusted proportionally the estimated reduction in unnecessary antibiotic prescribing corresponding to each participation level. In the realistic scenario, the reduction decreased from 9.7% to 7.9% when assuming 60% participation (sensitivity analysis 2A) and increased to 10.5% when assuming 80% participation (sensitivity analysis 2B). In the optimistic scenario, the corresponding values were 16.1% and 21.5%, respectively, compared with a base-case value of 19.9%. The third sensitivity analysis varied the assumed duration of the intervention effect to six months (sensitivity analysis 3A) and 24 months (sensitivity analysis 3B), respectively (compared with the 12 months assumed duration in the base case). Finally, in sensitivity analysis 4, we present the results excluding AMR-related costs. The latter analysis was conducted to account for the fact that ecological correlations between average antibiotic consumption and resistance used in the Shrestha et al. approach might not identify the causal effect of use on resistance. In addition, according to a study by Rahman et al. [25], effects of usage on resistance vary significantly across different drugs and bacteria, and, more importantly, while increases in antibiotic use were found to immediately and persistently increase resistance, decreases in usage had little to no observable effect on resistance. This makes it very difficult to translate resistance dynamics into our short-term estimates, and therefore we explore the impact of removing this uncertain economic impact from our analysis.

Results

Table 1 presents the cost per GP of the intervention implemented in the HAPPY PATIENT project, broken down by type of cost and country. Notably, fixed and variable costs by group exhibit the greatest variation among TCs, while variable costs remain relatively consistent. In terms of total intervention costs, France and Lithuania incur the highest

Table 1 Cost of the interventions per GP by cost component

Country	Intervention cost per GP (€)			
	(Upfront) fixed cost	Variable cost by group	Variable costs by GP	Total Intervention Cost
France	1.07	8.94	430.44	440.45
Greece	12.45	6.12	334.97	353.53
Lithuania	23.92	7.04	392.56	423.52
Poland	4.54	2.51	359.27	366.31
Spain	1.08	5.97	408.65	415.71
MEAN	8.61	6.12	385.18	**399.90**

costs (€440.5 and €423.5 per GP, respectively), while Greece has the lowest (€353.3). The average cost per GP across the five countries is estimated at €399.0.

Table 2 shows the mean, minimum and maximum unit cost per RDD for each ATB by ATB class and across the five TCs. However, cross-country price differences should be interpreted with caution, particularly for Lithuania, which is the only country for which retail prices were used in some cases (Penicillins V/Pivmecillinam, Fosfomycin, Trimethoprim ± Sulphonamides, and Macrolides/Clindamycin), whereas France, Greece, Poland and Spain provide reimbursed or reference prices. Table 3 details the calculation of the probability of AEs by ATB class. The first column lists the ATBs from Shehab et al. [7], the middle column provides the probability and confidence interval for experiencing an AE, and the last column shows the equivalent ATB class included in the APO chart of the HAPPY PATIENT project. AE likelihood varies notably across ATB classes: Nitrofurans exhibit the highest probabilities, approaching 1%, while Macrolides and Clindamycin show the lowest, around 0.1%.

Table 4 shows the unit costs of an outpatient visit and a hospital day in each TC to measure the cost of these AEs, together with minimum and maximum values extracted from the WHO publication. Again, notable cross-country differences are observed, with France and Lithuania generally incurring higher healthcare costs (€534.05 and €505.76 per inpatient day; €55.18 and €64.46 per outpatient visit, respectively), while Poland has the lowest costs (€143.82 per inpatient day and €17.16 per outpatient visit).

Combining data from Tables 2, 3, and 4, Table 5 consolidates information and provides a summary of the cost per ATB prescription for each TC. Specifically, the second column represents the average medicine cost per prescription, calculated by multiplying ATB daily dose cost by class (Table 2) by the number of treatment days registered in the APO charts; the third column captures the costs associated with AEs, calculated as per Eq. 1; the fourth column reflects the costs attributed to AMR, as determined by Eq. 3; and the final column presents the total cost of ATB per treatment, aggregating all these factors. A notable variation is observed across TCs, with Lithuania exhibiting the highest total cost per prescription at €21.92, while Spain has the lowest at €6.98. The average cost per prescription across countries is estimated at €12.0, with approximately 82% of this amount attributed to medication costs, around 17% to AMR-related costs, and less than 1% to AE-related costs.

Finally, Table 6 presents the extrapolated estimates at the national level for each of the 27 EU member states as described in Sect. 2.2.3. Cyprus and Malta were excluded due to data unavailability. The first column presents the estimated costs of implementing the HAPPY PATIENT

Table 2 Minimum, average and maximum unit cost per ATB RDD by class and country

Cost of ATBs per recommended daily dose, by class and country (€)

ATB drug or class	France			Greece			Lithuania			Poland			Spain		
	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max
Penicillins V or Pivmecillinam	0.95	1.26	1.56	1.70	1.70	1.70	4.67	4.67	4.67	0.15	0.15	0.15	0.82	0.82	0.82
Amoxicillin	0.55	0.55	0.55	0.30	0.30	0.30	0.46	0.46	0.46	0.26	1.61	4.56	0.29	0.29	0.29
Amoxicillin-clavulanic acid	1.73	1.73	1.73	0.99	0.99	0.99	5.58	5.58	5.58	1.21	1.21	1.21	1.02	1.02	1.02
Fosfomycin	5.23	5.23	5.23	2.63	2.63	2.63	11.46	11.46	11.46	4.56	4.56	4.56	2.50	2.50	2.50
Nitrofurantoins	1.12	1.12	1.12	0.62	0.62	0.62	1.04	1.04	1.04	0.43	0.43	0.43	0.86	0.86	0.86
Trimethoprim ± Sulphonamides	0.33	0.99	1.65	0.58	0.58	0.58	0.28	0.59	0.89	0.39	0.80	1.22	0.23	0.38	0.54
Macrolides or Clindamycin	0.78	1.87	3.29	1.05	1.31	1.70	0.77	1.65	2.44	0.38	0.82	1.09	0.58	1.32	1.87
Cephalosporins	1.50	2.93	9.18	1.00	1.05	1.10	1.48	1.55	1.59	1.39	1.41	1.43	1.15	2.36	4.00
Quinolones	1.31	3.62	8.13	0.67	0.89	1.19	1.38	1.38	1.38	0.65	0.65	0.65	0.47	1.43	2.72
Other ATBs	0.43	2.19	6.78	0.35	0.35	0.35	0.37	0.37	0.37	0.24	0.24	0.24	0.27	0.62	0.97

Table 3 Probability of AEs by ATB

ATB	Probability of an AE [95% CI]*	ATB in HAPPY PATIENT APO Chart
Amoxicillin and Penicillin	0.00155 [0.00123–0.00187]	Amoxicillin and Penicillin V or Pivmecillinam
Amoxicillin-Clavulanate	0.0078 [0.0055–0.00102]	Amoxicillin-Clavulanate
Nitrofurans (nitrofurantoin)	0.0097 [0.0058–0.00135]	Nitrofurans (Nitrofurantoin)
Sulphonamides and Trimethoprim	0.00189 [0.00131–0.00247]	Trimethoprim and Sulphonamides
Macrolides, Ketolides and Lincosamides (Clindamycin)	0.00118 [0.00795–0.00157]	Macrolides or Clindamycin
Cephalosporins	0.0061 [0.0045–0.0077]	Cephalosporins
Fluoroquinolones	0.0092 [0.0070–0.00115]	Quinolones
Unspecified and other ATBs	0.00147 [0.0096–0.00198]	Fosfomycin and Other ATBs

*Source: Shehab et al., 2008. Notes: *CI* confidence interval

Table 4 Country-specific data of unit costs (€) of hospitalization and outpatient consultations

Unit costs of healthcare visits (€)* [minimum – maximum]					
	Country				
	France	Greece	Lithuania	Poland	Spain
Costs of inpatient day	534.05 [512.32–690.69]	303.46 [291.10–392.45]	505.76 [485.16–654.07]	143.82 [137.96–185.99]	409.27 [392.61–529.30]
Cost of outpatient visit	55.18 [48.44–57.54]	33.73 [29.66–35.16]	64.46 [56.56–67.10]	17.16 [15.58–18.49]	43.56 [38.20–45.38]

*Source: WHO, 2010 – updated to 2022 prices

Table 5 Mean cost per prescription by type

Country	Mean ATB cost per prescription (€) [min–max]			
	ATB Medication	AEs	AMR	Total
France	5.94 [4.78–8.26]	0.20 [0.12–0.34]	3.22 [1.82–3.93]	9.36 [6.72–12.53]
Greece	9.48 [8.65–10.71]	0.09 [0.05–0.16]	4.50 [2.54–5.49]	14.07 [11.24–16.36]
Lithuania	20.82 [20.36–21.22]	0.19 [0.11–0.32]	0.91 [0.52–1.11]	21.92 [20.99–22.65]
Poland	8.18 [5.62–13.03]	0.04 [0.02–0.06]	1.21 [0.68–1.48]	9.43 [6.32–14.57]
Spain	5.45 [4.46–6.57]	0.14 [0.08–0.23]	1.39 [0.78–1.69]	6.98 [5.32–8.49]
Mean	9.83 [8.44–12.19]	0.11 [0.065–0.19]	2.06 [1.16–2.50]	12.00 [9.67–14.88]

interventions in general practice settings across each EU member, assuming a GP participation rate of 74%. As shown in Table 1, intervention costs contain a significant proportion of variable costs, meaning that larger countries with a higher number of GPs incur greater overall intervention costs. The total estimated cost of implementing these interventions EU-wide is approximately €107 million.

The second column indicates the estimated annual number of potentially unnecessary ATB prescriptions in each country, with an EU-wide estimate of 239 million potentially unnecessary prescriptions issued by GPs each year. The third column shows the economic burden of these potentially unnecessary prescriptions. It is estimated that across European healthcare systems, 2.7 billion euros are spent each year on potentially unnecessary ATBs prescribed by GPs.

The following columns provide projections for reducing these unnecessary prescriptions under the two described scenarios: a realistic scenario (9.7% reduction), where an estimated 23 million annual prescriptions could be avoided across the EU, and an optimistic scenario (19.9% reduction), with a potential reduction of 47.5 million prescriptions annually.

Based on these reductions, the estimated economic savings range from €258 million in the realistic scenario to €529 million in the optimistic scenario per year. After deducting the intervention costs (detailed in the second column), the potential net savings for the EU are €151 million in the realistic scenario and €423 million in the optimistic scenario.

The results of the sensitivity analyses are presented in Supplementary online material 3. Across all scenarios, the interventions continued to generate net healthcare savings. Varying the duration of the intervention effect had the greatest influence on the results: under the realistic scenario, estimated net savings decreased to €22 million when assuming a six-month effect, and increased to €409 million when assuming a two-year effect. The combined effect of varying drug unit costs, AE probabilities and healthcare visits costs led to an estimated net saving of 90 million when using the conservative values and to an estimated net saving of 224 million when using the highest values, both under the realistic scenario. Changes in GP participation rates had the smallest impact on the results, as participation influences both intervention costs and the reduction in unnecessary antibiotic prescribing: net savings in the realistic scenario ranged from €122 million (60% participation) to €164 million (80% participation). Finally, excluding potential savings from reductions in AMR resulted in net savings of €87 million and €291 million under the realistic and optimistic scenarios, respectively.

Discussion

This study shows the substantial economic burden placed on European healthcare systems by potentially unnecessary ATB treatments prescribed in general practices. Across the EU, an estimated 2.7 billion is spent each year on healthcare

Table 6 Main results (intervention costs, potentially unnecessary ATB prescriptions and associated potential savings)

Country	Intervention cost (€)	Potentially unnecessary ATB prescriptions	Cost of potentially unnecessary ATB prescriptions (€)	Reduction in potential unnecessary ATB prescriptions		Potential savings (€)		Potential net savings (saving - intervention costs) (€)	
				Realistic scenario	Optimistic scenario	Realistic scenario	Optimistic scenario	Realistic scenario	Optimistic scenario
France	21,520,205	54,464,032	509,783,198	5,283,011	10,838,342	49,448,970	101,446,856	27,928,766	79,926,652
Greece	1,017,127	6,365,680	89,555,576	617,471	1,266,770	8,686,891	17,821,560	7,669,763	16,804,432
Lithuania	799,378	1,127,064	24,700,099	109,325	224,286	2,395,910	4,915,320	1,596,532	4,115,942
Poland	2,915,082	25,690,992	242,248,866	2,492,026	5,112,507	23,498,140	48,207,524	20,583,058	45,292,443
Spain	12,955,260	31,397,863	219,166,411	3,045,593	6,248,175	21,259,142	43,614,116	8,303,882	30,658,856
Austria	1,980,087	2,219,384	30,789,594	215,280	441,657	2,986,591	6,127,129	1,006,503	4,147,042
Belgium	4,209,127	6,381,351	77,103,843	618,991	1,269,889	7,479,073	15,343,665	3,269,945	11,134,537
Bulgaria	1,166,135	5,259,107	54,557,774	510,133	1,046,562	5,292,104	10,856,997	4,125,969	9,690,862
Croatia	680,865	2,148,013	24,621,717	208,357	427,455	2,388,307	4,899,722	1,707,441	4,218,856
Czechia	2,261,632	4,151,958	51,650,058	402,740	826,240	5,010,056	10,278,361	2,748,424	8,016,730
Denmark	1,391,881	2,540,604	27,871,946	246,439	505,580	2,703,579	5,546,517	1,311,698	4,154,636
Estonia	281,399	397,770	4,075,804	38,584	79,156	395,353	811,085	113,954	529,686
Finland	2,275,650	1,790,435	19,174,548	173,672	356,297	1,859,931	3,815,735	−415,719	1,540,085
Germany	17,846,062	23,146,081	306,712,561	2,245,170	4,606,070	29,751,118	61,035,800	11,905,056	43,189,738
Hungary	1,144,895	3,592,349	45,376,353	348,458	714,877	4,401,506	9,029,894	3,256,611	7,884,999
Ireland	1,269,795	2,831,482	39,622,233	274,654	563,465	3,843,357	7,884,824	2,573,561	6,615,029
Italy	11,889,200	32,424,189	508,544,298	3,145,146	6,452,414	49,328,797	101,200,315	37,439,596	89,311,115
Latvia	432,193	656,829	6,849,617	63,712	130,709	664,413	1,363,074	232,220	930,881
Luxembourg	171,892	323,486	5,023,140	31,378	64,374	487,245	999,605	315,352	827,713
Netherlands	4,791,219	4,589,564	49,493,147	445,188	913,323	4,800,835	9,849,136	9,617	5,057,918
Portugal	8,354,683	4,868,800	72,973,223	472,274	968,891	7,078,403	14,521,671	−1,276,280	6,166,989
Romania	3,648,797	15,885,635	169,837,133	1,540,907	3,161,241	16,474,202	33,797,589	12,825,405	30,148,793
Slovakia	1,247,828	2,705,328	35,686,140	262,417	538,360	3,461,556	7,101,542	2,213,728	5,853,714
Slovenia	382,750	629,356	8,481,698	61,048	125,242	822,725	1,687,858	439,974	1,305,108
Sweden	1,875,372	3,121,818	34,757,721	302,816	621,242	3,371,499	6,916,786	1,496,127	5,041,414
TOTAL EU	106,508,514	238,709,170	2,658,656,700	23,154,790	47,503,125	257,889,700	529,072,683	151,381,186	422,564,169

resources due to ATBs potentially misused. These figures do not include direct patient costs or indirect costs, such as patients' out-of-pocket expenses or forgone productivity associated with premature mortality and morbidity due to AEs and AMR caused by ATBs.

Given the effectiveness of the HAPPY PATIENT interventions in general practices, we assessed the potential economic impact and scalability of the interventions across the EU. Our analysis considered two scenarios: a realistic scenario—assuming an approximate 10% reduction in potentially unnecessary ATBs—where the projected net savings would reach €151 million, and an optimistic scenario—assuming an approximate 20% reduction—where net savings could amount to €423 million across the EU. The results demonstrate that, over and above the expected improvements on patient outcomes resulting from minimising AEs and mitigating AMR, reducing unnecessary ATB prescriptions also generates significant economic savings for healthcare systems. Scaling these interventions across the EU could lead to substantial reductions in ATB overuse and healthcare costs. Although considerable uncertainty remains around our estimates, the sensitivity analyses conducted indicate that substantial savings are highly plausible across a wide range of assumptions.

Previous research has already highlighted the effectiveness of public campaigns and antimicrobial stewardship programs in European settings in reducing unnecessary antibiotic use. In this sense Filippini et al. [26] demonstrated that public campaigns may reduce antibiotic consumption by 6.5–28.3%, emphasising their value as an intervention strategy. In the same line, several studies have been conducted in individual European countries, confirming that interventions aimed at reducing antibiotic misuse can be effective. However, these studies do not incorporate cost analyses [23, 27–31] or they are restricted to single-country settings and specific healthcare environments [32–35].

Little et al. [36] conducted a study across six European countries and found that training in point-of-care C-reactive protein (CRP) testing, communication skills, or both significantly reduced the likelihood of antibiotic prescriptions by GPs by 47%, 32%, and 62%, respectively, compared to usual care. Building on this, Oppong et al. [37] evaluated the cost-effectiveness of these training programs. Their analysis identified communication skills training as the most cost-effective strategy, leading to a 31.3% reduction in antibiotic prescribing compared to usual care (59.61% vs. 40.95%). Notably, this reduction exceeds our optimistic scenario, which estimates a 19.9% decrease. However, it is important to highlight that our estimates specifically reflect reductions in antibiotic prescriptions deemed potentially unnecessary, not total ATB prescriptions, which is arguably more policy-relevant.

Our study also complements previous research by addressing aspects that have not been examined before. Specifically, we estimated the cost of unnecessary antibiotic prescriptions in general practice across five European countries, and evaluated the country-level potential savings generated by a multifaceted intervention in these countries. Furthermore, we scaled up our findings, projecting the potential reduction in unnecessary antibiotic prescriptions and the corresponding cost savings at a European-wide level.

It is important to emphasise that this analysis required a series of assumptions. Detailed information was only available for the five countries participating in the HAPPY PATIENT project. Consequently, projections for the remaining EU member states were sometimes derived from extrapolations based on mean values obtained from these five countries. Extrapolations were made for the unit costs of drugs, the cost of the intervention per GP, the average duration of antibiotic treatments, the percentage of potentially unnecessary prescriptions issued by general practitioners, and the effectiveness of the evaluated interventions. While variations in these parameters are anticipated across different countries, the use of mean values from regions that also exhibited considerable variability offers a level of confidence, particularly in the aggregated projections at the European level.

However, we acknowledge that general practice physicians' prescribing behaviours vary widely across and even within EU countries. Factors influencing prescriptions, such as local healthcare guidelines, levels of diagnostic support, and patient expectations, could impact the intervention's applicability and success. This variation may affect the projected cost savings at the EU level. On the other hand, this study focuses on direct healthcare costs only, indirect costs such as lost productivity associated with ATB-related AEs and AMR were not included. These costs can be significant, particularly for conditions requiring longer-term care and those that yield to premature deaths, potentially underestimating the intervention's total economic impact. Finally, it is important to note that any intervention that reduces antibiotic prescribing could theoretically also lower prescribing in situations where treatment is clinically indicated. The IMAGINE interventions were, however, specifically designed to support clinical decision-making and improve diagnostic accuracy, rather than to reduce overall ATB prescription. For this reason, while such unintended effects cannot be entirely ruled out, we expect any reduction in necessary prescriptions to be minimal.

Given the urgent need to reduce AMR across Europe, there is a call to implement effective interventions within each European state [26, 38]. However, the successful implementation of such measures at the EU level may depend on a strong commitment from European institutions to lead and coordinate these efforts. Organisations such as the European Centre for Disease Prevention and Control (ECDC) or the World Health Organization Regional Office for Europe (WHO/Europe) might be well-positioned to oversee a comprehensive European strategy that integrates interventions shown to be effective in reducing antibiotic prescriptions. If the responsibility for these interventions were left primarily to national authorities, there is a risk that responses would vary significantly across Europe, potentially limiting the benefits of a more coordinated, pan-European approach.

An essential consideration is that implementing these interventions requires allocating the necessary resources by health authorities and/or relevant institutions. As these estimates indicate, the resources required to implement these interventions are substantial. However, this analysis also demonstrates that the resulting savings would significantly exceed the initial investment. Therefore, authorities must recognise the potential savings when allocating resources to support these initiatives.

Given the nature of the proposed interventions, an additional key consideration is the willingness and motivation of healthcare professionals to engage with them. In the HAPPY PATIENT project, participation was voluntary, which likely contributed to higher levels of engagement among those who self-selected to participate. However, professionals who would derive the greatest benefit from such interventions might also be those least likely to engage voluntarily, posing a challenge for broader implementation. Overcoming this barrier is critical, as increasing participation could yield greater improvements in prescribing behaviours than those observed in the HAPPY PATIENT project.

In addition to the focus on primary care, it is important to recognise the critical role of antibiotic use within hospital settings, particularly among high-risk groups such as immunosuppressed and oncological patients, for whom inappropriate antibiotic use can lead to severe clinical consequences. Targeted and judicious antibiotic use in hospitals is therefore also essential, as rising AMR directly contributes to increased in-hospital morbidity, longer lengths of stay, higher treatment complexity and greater healthcare utilisation. Furthermore, insufficient reimbursement for many antibiotics may create misaligned incentives for healthcare providers, potentially discouraging the optimal use of narrow-spectrum or newer agents. Addressing these structural barriers, alongside strengthening stewardship efforts in both primary care and hospital settings, will be key to reducing antibiotic overuse and mitigating the broader clinical and economic burden of AMR.

In conclusion, this analysis shows the potential substantial economic benefits associated with interventions that reduce unnecessary ATBs prescribed in general practice. Their success relies on strong institutional commitment, sufficient resources, and professional engagement. With these in place, these types of interventions could play a crucial role in addressing one of the most urgent healthcare challenges.

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Declarations

Competing interests The authors declare that they have no conflicts of interest.

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