Is There a Difference between the Willingness to Pay for Antimicrobials and Other Curative Treatments? A Cost per Cure Analysis of Curative Therapies in Spain

113762

ISPOR EUROPE 2021
30 November - 3 December

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Background & Objectives

Antimicrobial resistance is a growing global healthcare priority requiring continuous development of new antimicrobials, which continues to be challenging due to disinvestment for decades. The World Health Organization (WHO) has highlighted the increasing prevalence of antibiotic resistance [1, 2]. In 2017, the WHO published a list of bacteria for which new antibiotics were urgently needed [5], in particular the group of pathogens referred to as the critical priority pathogens, 6 pathogens with increasing multi-antibiotic resistance and virulence. However, a pharmaceutical pipeline analysis of new antibiotics suggests that antibiotic incentives and initiatives have not sufficiently promoted the research and development (R&D) of innovative antibiotics [3].

Even though antibiotics are the first class of drugs that were able to cure a disease [7], less R&D has been focused on antimicrobial treatments [8], while other therapy areas have benefitted from significant R&D. The R&D in cancer drugs has grown substantially in the last 25 years, thereby contributing almost 40 percent of the global clinical pipeline [9]. The O'Neill report on issues related to tackling drug-resistant infections globally estimated that based on trends in 2016 and if not addressed, by 2050, antimicrobial resistance will account for 10 million deaths globally, compared to 8.2 million cancer-related deaths and 1.2 road traffic accident-related deaths [10]. As the number of marketed oncology products, orphan drugs and other chronic disease treatments (e.g. diabetes, hypertension) have increased, so too has the scrutiny on clinical outcomes and treatment benefits by the health technology assessment (HTA) bodies that perform the reimbursement analyses and decisions. In the short-term, the budget impact of curative therapies may seem large because the costs are all accrued in a short period, unlike treatments for chronic diseases where their budget impacts can be substantial over the total duration of treatment which can be for many years.

In Spain, several antibiotic stewardship initiatives and policies have been developed 4, 5. Notably, a consensus document on antimicrobial stewardship highlights that antimicrobial agents are unique in that their efficacy is higher than any other drugs in respect of their benefits on morbidity and mortality, and that antimicrobials are prescribed by almost all medical specialties 6.

This study aimed to understand the differences in observed willingness to pay between antimicrobials and other curative therapies by the healthcare system in Spain, by analysing the cost of treatment to achieve a cure, across different therapeutic areas. We also sought to ascertain the key drivers that affect the cost per cure metric.

Methods

A stepwise process was used to assess the cost per cure per licensed therapeutic indication in Spain for adult treatments:

- "Cure" was defined as the eradication or resolution of the condition in patients, after permanent discontinuation of treatment if it was used for one year or less and occurred in ≥ 10% of the patients; each indication for drugs with multiple indications was assessed individually.
- The list of all approved drugs in Europe was downloaded from the European Medicines Agency (EMA) website from 1st January 2010 until 25th December 2020 [9].
- Only branded medicinal products were considered: generics and biosimilars alternatives were excluded.
- Other exclusion criteria were: Metastatic cancer or locally/regionally advanced cancers; Adjuvant/neoadjuvant treatments; Treatments for chronic conditions; Vaccines and prophylactic treatments; Paediatric treatments; Surgical, diagnostic and medical devices.
- The list of authorised drugs was assessed by 2 assessors to define a shortlist of drugs considered curative.
- Each product Summary of Product Characteristics (SmPC) was reviewed to extract all of the licensed indications for each drug. Only indications that comply with the definition of cure were considered; when applicable, different subgroup of patients were also considered if the posology or treatment duration differed.
- Listed Drug prices were extracted from the public reference sources for prices in Spain and ex-factory prices were included.
- The cure rates for each drug were extracted from the pivotal clinical studies for each indication on a clinical endpoint relevant for that condition, reported in the SmPC or the European public assessment report (EPAR). Table 1 summarises the endpoints used to describe the cure per indication.
- The average treatment cost per patient for each indication was calculated based on the standard treatment plans described in the SmPCs in terms of dose, posology and length of therapy for each indication. Cost of treatment for drugs that are used in combination with other drugs as recognised curative treatment regimens were also considered, but no other healthcare resource utilisation was accounted for in this analysis.
- The cost per cure outcome was derived using the total treatment cost and cure rate, and categorised by therapeutic area.
- An Advisory Board with external clinical and payer experts was conducted to validate the design and discuss the outcomes if this analysis

Results

The list of drugs downloaded from the EMA website included 1,502 approved medicines for human use. Triage of those that are generics or biosimilars resulted in a list of 1,179 drugs, and on applying the additional inclusion and exclusion criteria, 32 drugs were identified as cures, of which 24 were reimbursed in Spain and for which prices were available at the time of the study. The summary of the drugs included in this study is in the table 1.

Table 1: Drugs included in the study, with the clinical study endpoints

Generic name	Indication	Cure endpoint
brentuximab vedotin	Lymphoma, Hodgkin previously untreated; Lymphoma, Systemic anaplastic large cell	CR
isavuconazole	Invasive Aspergillosis; Mucormycosis	CR
delamanid	Tuberculosis, Multidrug-Resistant	CR(SCC)
fidaxomicin	Clostridium Infections	CR(GCR)
sofosbuvir / velpatasvir	Chronic hepatitis C	SVR12
obinutuzumab	Leukemia, Lymphocytic, Chronic, B-Cell	CR
ledispavir / sofosbuvir	Chronic hepatitis C	SVR12
ertapenem	Bacterial infections (Community-Acquired pneumonia; Abdominal; Gynaecological; Diabetes-related foot)	CR(M)
tisagenlecleucel	B-Cell Acute Lymphoblastic Leukemia; Lymphoma, Large B-Cell, Diffuse	CR
glecaprevir / pibrentasvir	Chronic hepatitis C	SVR12
gemtuzumab ozogamicin	Leukemia, Myeloid, Acute	CR
midostaurin	Leukemia, Myeloid, Acute	CR
tedizolid phosphate	Soft Tissue Infections	CR(M)
sofosbuvir	Chronic hepatitis C	SVR12
venetoclax	Chronic lymphocytic leukemia	CRi
ombitasvir / paritaprevir / ritonavir	Chronic hepatitis C	SVR12
sofosbuvir / velpatasvir / voxilaprevi	Chronic hepatitis C	SVR12
dalbavancin	Bacterial infections (Soft Tissue; Skin)	CR(M)
axicabtagene ciloleucel	Lymphoma, Large B-Cell, Diffuse	CR
ceftazidime / avibactam	Bacterial infections (Pneumonia (HAP & VAP); Urinary Tract; Complicated Intra-abdominal)	CR(M)
elbasvir / grazoprevir	Chronic hepatitis C	SVR12
ceftolozane / tazobactam	Bacterial infections (Complicated intra-abdominal; Complicated urinary tract; Acute pyelonephritis)	CR(M)
ceftaroline fosamil	Bacterial infections (Skin and soft tissue; Community-acquired pneumonia)	CR(M)
Imiquimod	Keratosis	CR(S)

CR	*Complete response/complete remission*	*CR+CRi*	*Complete response & incomplete response*
CR(GCR)	*Global cure rate (Clostridium difficile)*	*CRi*	*Response - incomplete*
CR(M)	*Microbiological response*	*CR(SCC)*	*Sputum culture conversion (tuberculosis)*
SVR12	*Sustained virologic response at 12 weeks (hepatitis C)*	*CR(S)*	*Clinical cure rate of the skin*

Curative therapies were mainly treatments for haematologic cancers and anti-infectives. The cure rates were highest for hepatitis C treatments (over 85% SVR at 12 weeks) accounting for the different regimens and treatment durations for the different genotypes.

The average cost per cure for all the indications included in this study in Spain was €52,719 but with a wide range (range: €107 - €791k). The cost per cure for the haematological cancers with a very broad range (€54k - €791k) and substantially higher than the cost per cure for all other conditions. When analysing by therapeutic area, the the cost per cure for the haematological cancers was highest (regardless of considering leukaemias or lymphomas) with a very broad range (€53k - €790k) and substantially higher than the cost per cure for all other conditions. Within the haematological drugs, the cost/cure was particularly high for the CAR-T treatments (€667,471). The average cost per cure for the oncology treatments, hepatitis C drugs and other anti-infectives (antibiotics, antifungals) was €284,256, €43,951, and €5,617, respectively. The average cost per cure for antibiotics, excluding treatments for multi-drug resistant tuberculosis, was €2,274 (range: €107 - €8,042), which means that on average, to achieve a cure with an antibiotic, payers in Spain pay €2,274. The anti-infectives had the lowest cost per cure across all therapeutic areas analysed, and within these, antibacterials had the lowest average cost per cure. The cost per cure for the one treatment for multi-drug resistant tuberculosis was €22,885. The average cost per cure for the hepatitis C treatments ranged widely from €20,890 for patients without cirrhosis (Genotype 4) to €104,598 for patients ineligible or intolerant to peginterferon alfa (Genotype 1), with some hepatitis C treatments being administered in combination regimens. Overall, keratosis and the anti-infectives had the lowest cost per cure across all therapeutic areas analysed, and within these, antibacterials had the lowest cost/cure in Spain.

The average duration of treatment for the drugs included in this study varied significantly. With the exception of the CAR-T treatments, oncology drugs had the longest duration of treatment, compared to an average of 12 weeks for hepatitis C treatments. The duration of treatment for the antibiotics ranged from 1 dose (dalbavancin hydrochloride) to 10 days with an average of 8.3 days (median: 7 days).

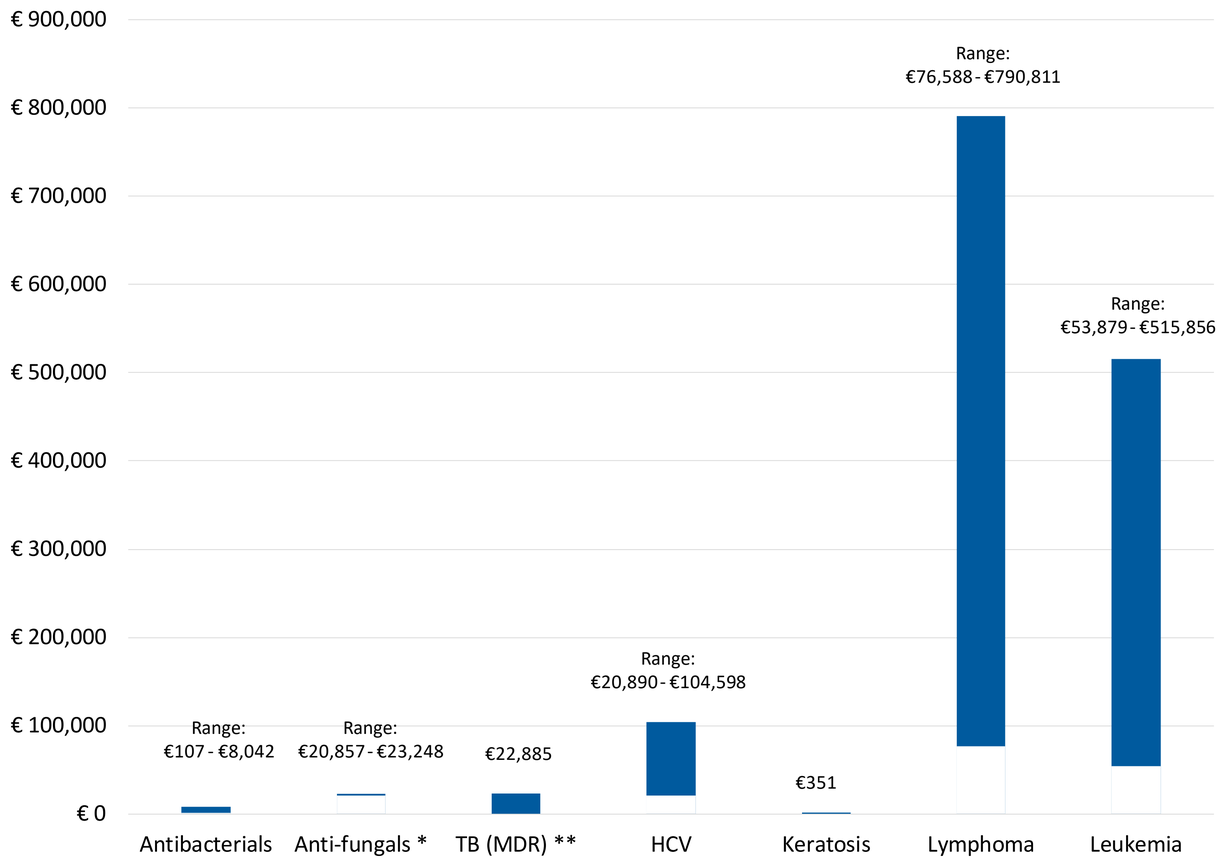
Budget impact and patient numbers are important factors to consider when securing pricing, so an analysis stratifying by Orphan designation was done. Of the 24 drugs included, 8 were orphan drugs, of which 3 drugs each have 2 reimbursed indications. The average cost per cure for the 8 orphan drugs included in the study, of which some have more than one indication, was €225k.

The summary of the drugs included in the study are listed in Table 1 which includes the endpoints from the clinical studies for the drugs.

The cost per cure ranges are shown in Figure 1.

Results (cont.)

Figure 1: Average cost per cure across different therapeutic areas, in Spain



**Two drugs with a very close range cost per cure* ***One drug only*

HCV: Hepatitis C *TB (MDR): Tuberculosis, multi-drug resistant*

Lymphoma includes: Hodgkin lymphoma (previously untreated), systemic anaplastic large cell lymphoma (treatment-naïve), Chronic lymphocytic B-Cell Lymphoma, Follicular lymphoma, Large B-Cell, diffuse lymphoma.

Leukemia includes: Precursor cell lymphoblastic leukemia, myeloid leukemia, acute myeloid leukemia, chronic lymphocytic leukemia.

Discussion

This study sought to establish what the cost per cure for different therapeutic areas in Spain is. A significant variability across therapeutic areas was observed, and the cost per cure for antibacterials was considerably lower than that of oncology treatments (the highest). This significant variance can be explained by longer treatment durations and in some situations, by the higher prices of the drugs, or by the relatively lower clinical cure rates, reflecting the different characteristics of the diseases in the oncology setting.

Historically, antibiotics have been priced much lower than treatments for heart disease or cancer. With many antibiotics being off patent and therefore having a low price, many payers have come to expect that all new antibiotics will be priced similarly, even the innovative antibiotics that target multi-drug resistant pathogens [10]. The negative impact of this pricing expectation and the uncertainty of being reimbursed results in several companies having reduced their R&D in antibiotics[11, 12].

Generally, within reimbursement applications, antibiotics are assessed in the same way as other treatments and are expected to demonstrate that they provide better clinical outcomes than their existing comparator antibiotics [17]. However, microbiological data play a significant role in value demonstration, which is traditionally not recognised by payers as relevant information. Also, to protect their clinical effectiveness and minimise resistance, the new antibiotics are only used as a last resource, in a very small segment of the population, but without the incentives Orphan drugs have. Furthermore, clinical trials must have a non-inferiority design and are not in the population where these reserve antibiotics are expected to be used, which has implications for value demonstration for payers. Additionally, because antimicrobial resistance is a public health problem, the value to the general public in reducing the antimicrobial resistance could also be considered in reimbursement assessments[17].

The cost per cure is a simple but informative comparative analysis for curative therapies, however it has several limitations impact its results and conclusions:

- The use of list prices can significantly overestimate the costs for the healthcare system, introducing a significant limitation to the interpretation of the results of this analysis. During reimbursement discussions, confidential prices can, in many cases, be negotiated, where other factors are also considered, such as budget impact or country public health priorities. However, since these are confidential, any assumption made to estimate these could have introduce further bias to the analysis. Using the list prices was the most equitable option and the one is recommended to be used in gold standard cost-effectiveness analyses. But this is a significant limitation to the analysis; as an example, the cost/cure for each patient for hepatitis C treatments in this analysis ranged between €20k and €109k but in media reported prices, these were much lower than that [19].
- The overall patient size, was not accounted for directly in the current analysis. Budget impact and affordability are one of the most important factors analysed by payers when considering the introduction of a new drug; this may impact the drugs' price, with treatments for smaller populations having the potential for higher drug costs, given the limited budget impact; this is frequently observed for Orphan drugs. In this study, drugs that had orphan designation, for rare conditions, with small patient populations, had substantially higher average cost per cure compared to non-orphans, with far larger patient populations, of €225k and €40k, respectively. This reflects the different existing incentives (financial or of other nature) for bringing to the market innovative drugs for rare debilitating conditions with high unmet need, where the patient numbers are small, and the drugs are therefore rarely used
- In this analysis, different endpoints and time points were used to define cure, depending on the therapeutic area. This is observed also in other health economic analyses, such as cost-effectiveness, where all the different clinical endpoints from the different therapeutic areas are converted in a model to Quality Adjusted Life Years (QALYs) enabling comparison of products across therapeutic areas. The cost per cure is in a way a simplified version of this analysis for curative therapies, where cure rates group a variety of clinical endpoints, with possible different baseline risk of relapse, which is not accounted for in this analysis.
- Patient populations are different across therapeutic areas. Even though only drugs approved for adult patients were included, the mean age of the patients affected by the condition, and its impact on health related quality of life, progression and severity, and unmet medical need may differ between different therapeutic areas.
- Only medicines approved by EMA were included. Medicines approved via mutual recognition procedure as well as de-centralised and national procedures were not included.
- The cost per cure was based solely on the drug costs, and excluded any healthcare resource utilisation costs, and the results should be considered in this context.

Conclusion

Despite the limitations of this research, it highlights the wide variation in the cost per cure across different therapeutic areas. Antibiotics offer a significantly better cost per cure ratio than other treatments that are generally far more expensive and do not provide a comparable cost per cure. With the increasing disinvestment in the R&D of antibiotics, it may be worth considering implementing new reimbursement incentives to encourage R&D into novel, targeted antimicrobial treatments.

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This research is sponsored by Shionogi
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