



*Research article*

## **A Six Sigma DMAIC methodology as a support tool for Health Technology Assessment of two antibiotics**

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**Abstract:** Health Technology Assessment (HTA) and Six Sigma (SS) have largely proved their reliability in the healthcare context. The former focuses on the assessment of health technologies to be introduced in a healthcare system. The latter deals with the improvement of the quality of services, reducing errors and variability in the healthcare processes. Both the approaches demand a detailed analysis, evidence-based decisions, and efficient control plans. In this paper, the SS is applied as a support tool for HTA of two antibiotics with the final aim of assessing their clinical and organizational impact in terms of postoperative Length Of Stay (LOS) for patients undergoing tongue cancer surgery. More specifically, the SS has been implemented through its main tool, namely the DMAIC (Define, Measure, Analyse, Improve, Control) cycle. Moreover, within the DMAIC cycle, a modelling approach based on a multiple linear regression analysis technique is introduced, in the Control phase, to add complementary information and confirm the results obtained by the statistical analysis performed within the other phases of the SS DMAIC. The obtained results show that the proposed methodology is effective to determine the clinical and organizational impact of each of the examined antibiotics, when LOS is taken as a measure of performance, and guide the decision-making process. Furthermore,

our study provides a systematic procedure which, properly combining different and well-assessed tools available in the literature, demonstrated to be a useful guidance for choosing the right treatment based on the available data in the specific circumstance.

**Keywords:** Health Technology Assessment; Six Sigma; DMAIC; modelling; public health

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## 1. Introduction

Nowadays, the healthcare management is one of the major concerns in the private and public health field. To face its various and complex issues, in the literature, different managerial approaches have been proposed in the last years, to simulate and improve processes, to compare biomedical technologies and to aid clinicians in decision making. Among them, Health Technology Assessment (HTA) [1] and Six Sigma (SS) [2] proved to be reliable and promising approaches in the healthcare context. In particular, HTA is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the introduction and/or use of a health technology in a systematic, transparent, unbiased, and robust manner [3], as also established by the WHO [4]. HTA has been implemented also for the evaluation of pharmaceutical products [5,6], for example to compare, both qualitatively and economically, equivalent drugs, thus contributing to improve therapeutic quality and safety and, at the same time, to optimize drug procurement in hospital [5,6].

Besides, many HTA studies have also involved arrangements for reimbursement of drugs in different European and non-European countries. Reimbursement recommendations are guided by both clinical efficacy and cost-effectiveness [7]. In this context, the importance of choosing the right drug and the right dosage is witnessed by the literature [8,9]. However, it is important pointing out that, before making a decision on the acquisition of new health technologies or the adoption of new treatment protocols, hospital decision makers need a tailored analysis of the impact of this choice into the hospital workflow [10]. Shorr et al. [11] describe the impact of initially inappropriate antibiotic therapy on hospital Length Of Stay (LOS) in Gram-negative severe sepsis and septic shock. Interestingly, they show that initially inappropriate antibiotic therapy occurs in one-third of persons with severe sepsis and septic shock attributable to Gram-negative organisms. Beyond its impact on mortality, initially inappropriate antibiotic therapy is significantly associated with LOS in this population. Efforts to decrease rates of initially inappropriate antibiotic therapy may serve to improve hospital resource use by leading to shorten overall hospital stays [5]. Let us recall that different methodologies can be employed to comply with an HTA procedure; indeed, the tools and the data required for making a proper decision may differ from one setting to another [10].

In particular, in this paper, we propose the use of the SS DMAIC methodology, since it represents a systematic analytic procedure which could be generalized to a wide range of applications. The SS is a methodology that was initially introduced in the manufacturing sector and then in healthcare [12–14]. The SS is based on the so-called DMAIC cycle, which is articulated in 5 phases (Define-Measure-Analyse-Improve-Control), well established in the literature [15]. It has been successfully employed in the healthcare field, with applications to different processes and needs. Some papers published in the literature concern the application of SS, often combined with the Lean approach, to improve surgical processes by reducing hospitalization and waiting times, or improving operating rooms

efficiency [13,14,16–18]. Other applications regard the use of SS to guide the design and implementation of clinical pathways for specific patients' categories [19–21] or to provide a better management and control over healthcare-related infections [22–24]. Moreover, SS has been applied also to improve the perceived quality and patients' satisfaction [25,26]. The benefits of the SS methodology include cost reduction, customer satisfaction improvement and sales revenue growth [23,24]. Originally described as a method for variation reduction, the DMAIC cycle is applied in practice as a problem-solving tool, to improve the effectiveness of a given process or to enhance the performance in the delivery of healthcare services in a fast and standardized way [27,28]. From this point of view, the SS DMAIC cycle can represent a useful support tool for HTA [29], providing detailed analysis, evidence-based decisions, and efficient control plan.

Hence, in this study we exploit the SS DMAIC for the HTA of two antibiotics, Ceftriaxone and Cefazolin plus Clindamycin, with the aim of assessing their clinical and organizational impact in terms of postoperative LOS for patients undergoing surgery in the oral cavity. Our goal is to apply a combined methodology (SS and Multiple Regression) to assess the overall impact that two different antibiotics had on the healthcare organization. The LOS has been chosen as the measure of effectiveness in this study being an indicator of a broad range of clinical and organizational issues in a hospital. Indeed, the LOS is a direct index which affects the hospital costs as demonstrated in several works [30,31] and it is also the most used metric for assessing healthcare services and procedures, as outlined by the recent report from the General Directorate for Health and Food Safety (European Commission) of the European Union [32]. It is defined as the average number of days that patients spend in hospital, and can be also measured by dividing the total number of days stayed by all inpatients during a year by the number of admissions or discharges [33]. Therefore, the LOS reflects both the inefficiencies in surgical interventions that cause a prolonged stay, the pressure on the healthcare staff due to the growing workload and patients management tasks, and, not least, the increase in the healthcare expenditure generated by the costs per additional days of stay, whose analysis in the context of a novel HTA application was the specific goal of our study.

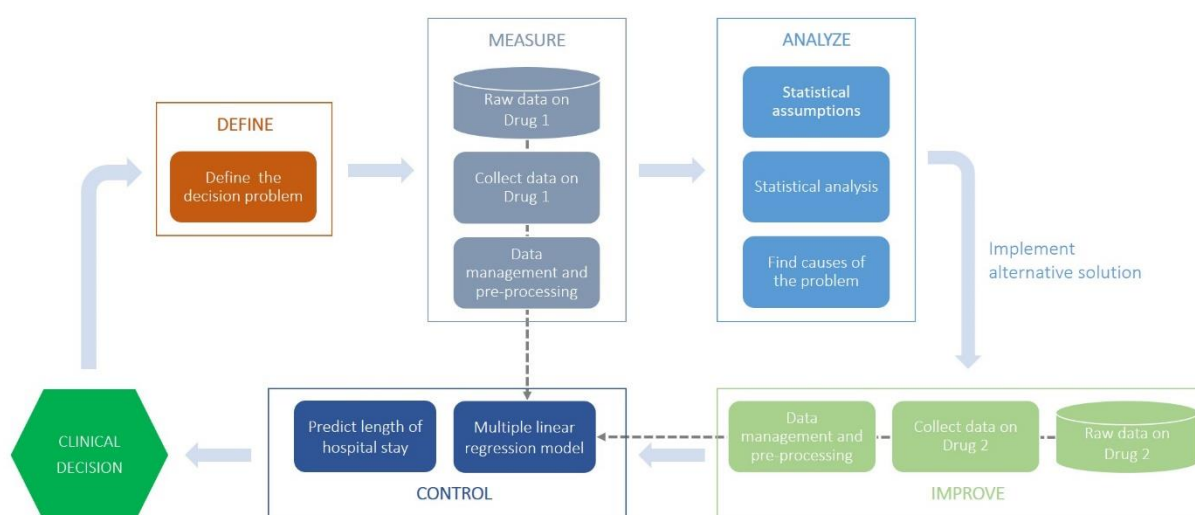
Here, as said, the DMAIC cycle, within the HTA framework, is devoted to the performance comparison between two antibiotics, in terms of the postoperative LOS of patients. We shall see that, in our peculiar application of DMAIC, the first three phases, namely Define, Measure and Analyse, follow the classical guidelines of the methodology; conversely, the Improve and Control phases are customized to our specific case, in a way that will be specified later. Through the DMAIC, it is possible to analyse the process in order to assess and compare the two alternatives and make the most appropriate decision. In addition, since the two antibiotics considered in this study share similar safety, legal, economic and technical profiles, the assessment procedure will be focused only on clinical and organizational factors, on which the final decision could then be based.

The novel contribution of our work goes in several directions. First, the HTA is often related to the purchase of medical devices or technologies [33]; in particular, the HTA studies related to drugs mainly involve arrangement for reimbursement [34]. In this study, instead, the effect of two drugs on managerial issues of the hospital is analysed. Then, as already mentioned, the SS DMAIC cycle is employed as tool to assess and compare two drugs (the two antibiotics in this case); from this point of view, it represents an innovative approach for HTA implementation. The performance comparison between the two drugs is obtained by using a given efficiency index (the postoperative LOS of patients, discussed above). Finally, the statistical analysis, required by the proposed SS DMAIC cycle, has been carried out into two phases and with the aid of a multiple linear regression technique, other than by the

classical statistical tests. In the analyse phase of the DMAIC cycle, the direct comparison between the two antibiotics, which allows to analyse the clinical efficacy, that in turn is a key issue of any HTA process, is performed; in the control phase, the regression analysis, aimed at analysing the organizational aspect of the HTA, is implemented. We processed the two phases separately since this has allowed us to predict the final LOS of each patient in advance, in order to analyse the impact on the organization of the hospital for each antibiotic. In particular, the development of a model based on the multiple linear regression technique, not only helped to confirm the results obtained by the statistical study conducted within the SS DMAIC analysis, but also allowed understanding, for each antibiotic, how much the postoperative LOS changes with respect to the variations of clinical and demographic factors.

## 2. Materials and methods

A SS DMAIC-based methodology for the implementation of the HTA of two antibiotics is proposed (Figure 1). Here, a multiple linear regression model is introduced in the Control phase of the DMAIC cycle to assess and compare the performance of the two drugs and their impact on the LOS for patients undergoing surgery for oral cancer.



**Figure 1.** Six Sigma DMAIC (Define, Measure, Analyse, Improve, Control) methodology for Health Technology Assessment.

Applying the DMAIC cycle to compare the performance of two antibiotics has primarily allowed us to clearly define the problem (Define), then to understand which data were necessary to conduct the study and how they had to be collected (Measure); subsequently, the implementation of statistical methodologies highlighted the variables which have the greatest influence on LOS for a given antibiotic (Analyse). The first three phases strictly follow the classical implementation of a DMAIC cycle; then, a new antibiotic has been introduced (in what can be considered the Improve phase), and it has been verified (within the Control phase) the differences in LOS between the two antibiotics.

Let us remember that the main aim of the research was to develop a tool capable of supporting

decisions regarding HTA, by considering that in the case under study the two antibiotics are comparable in terms of price, management, ethical issues etc.; hence, our attention can be focused only on the clinical and managerial efficacy. In this context, the tool we claim to develop is the employment of a methodology, Six Sigma, and a problem-solving strategy, DMAIC, in a new framework, i.e., the HTA. In the following of the section, after the description of the clinical case study, the application of the first four phases of the DMAIC process is described in detail.

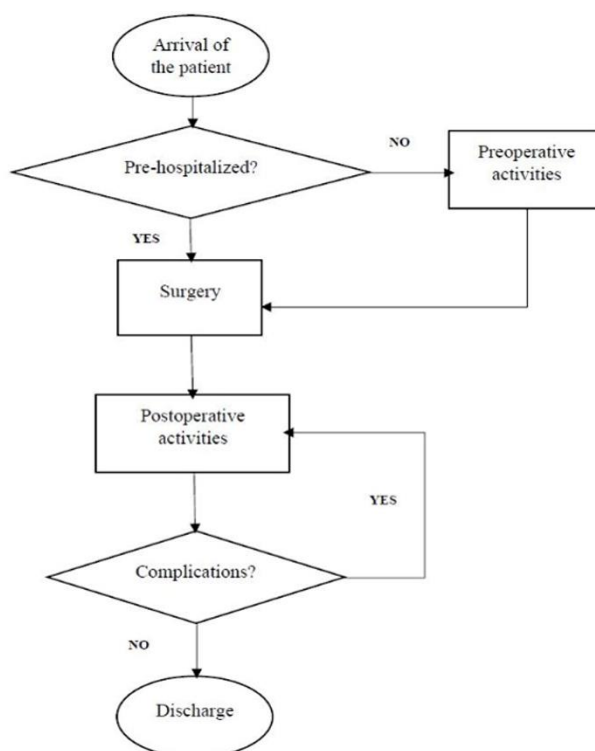
### *2.1. The clinical case study*

Tongue cancer belongs to the bigger group of oral cancer that currently represents the sixth most common cancer [35]. About 90% of cancers of the oral cavity is given by squamous cell carcinoma with a preferential localization on the tongue [36]. Tongue cancers are those malignant neoplasms that occur on the dorsal surface, ventral surface, borders and anterior part of the tongue. The incidence of tongue cancer is influenced by multiples variables, such as poor oral hygiene, persistent inflammations, smoking, alcohol abuse, and infections [37]. The incidence of these malignancies has increased during the last years [38] especially in young population.

In this study, we considered all surgeries that expected an exportation of the tongue [39] or part of it, with or without reconstruction. Surgical reconstruction is generally advised in those surgeries that need big tissue removal to restore the anatomy and/or the functionality of the tongue or to reduce oral disabilities. It is important to restore the phonatory and the swallowing ability to perform a correct management of these patients and guarantee a good quality of life [40]. Surgical options are primary closure or the use of local or free flaps to perform the reconstruction. The risk of bleeding and infection can be present due to damages to the blood vessels of the trachea during the tracheotomy. Nevertheless, tracheotomy is fundamental because it reduces the probability of incurring in complication postoperatively (i.e., bleeding and consequently death for suffocation).

Regarding the antibiotics, Ceftriaxone is a drug with antibacterial activity belonging to the group of third generation of cephalosporins. The methoxy group present in the structure of Ceftriaxone enhances the stability of the antibiotic against bacterial beta-lactamases and broadens its spectrum of action towards Gram-negatives. The triazine function is responsible for the increased permeability of the bacterial wall and the slow elimination of the drug from the body. Ceftriaxone seems more active in inhibiting the synthesis of the bacterial wall and the transpeptidase of cefazoline, cephalothin, cephalexin, cephaloridine, cephaloridine, cephaloridine, cephaloridine. In this study, the administration of the antibiotic is a possible post-operative activity.

Figure 2 schematically shows patients surgery pathway, from the acceptance to the discharge. Note that only patients with prehospitalization underwent surgery, since the other needed some preoperative activities. After the surgery or on the occurrence of any complications, postoperative activities, such as administration of antibiotics, are performed. Finally, when the patient is safe, he/she can be discharged.



**Figure 2.** Flow Chart of the clinical pathway for patients.

## 2.2. Define phase - development of the methodology

In the first phase of SS DMAIC, the purpose of the cycle is to define a multidisciplinary work team and plan the various analysis tasks. In our study, the team was composed of clinicians of the Maxillofacial Department of the University Hospital of Naples Federico II and biomedical engineers, each one with previous experience in health management. The team was responsible for collecting and analysing the data before and after the surgery of the tongue. The champion and the leader supervised and coordinated the study and gave a conceptual help to interpreting the data.

Initially, a project diagram was produced to define the problem to be solved:

- **Project title:** evaluation of a pharmacological therapy for tongue cancer.
- **Question:** finding the best antibiotic according to the postoperative LOS.
- **Critical to quality (CTQ):** postoperative LOS; it is defined as the number of days between the date of surgery and the date of discharge.
  - **Timeline:** the Define, Measure and Analyse phases started in January 2010, while the Improve and Control phases started in January 2011, with the introduction of another antibiotic. The project ended in December 2018.
  - **In scope:** Oral cavity surgery. Maxillofacial surgery at the University Hospital of Naples Federico II.
  - **Out of scope:** All the other structures, interventions, and drugs.
  - **Financial:** No funding was provided to reach the target.

A comment on the timeline may be necessary considering the length of the project: during the first three phases, the data regarding patients who received Ceftriaxone were collected; the improve

phase was the one designed to kick off the new protocol in the hospital, while the control phase gave us the chance to collect the data of patients who received Cefazolin plus Clindamycin and to analyse them. Nowadays, the collection and the processing of such an amount of data took a long time; nevertheless, it should be considered a strength of our work. In fact, a further development could be to perform data mining and machine learning analyses that could add value and open new analytical scenarios, such as the comparison of biomedical technology through artificial intelligence [41,42]. Across the whole timeline the administration of the antibiotics has always been independent from the study and from the authors, so that no bias has been introduced in the research work; besides, the patients had similar clinical characteristics. Indeed, the choice of the antibiotic to be administered to patients was dictated by the protocols followed by the hospital. Until 2011, the clinical guidelines suggested the use of Ceftriaxone as main antibiotic. Afterwards, as reported in section 2.5, according to the hospital guidelines and the evidence in literature, regarding the success of the coupling of a first/second generation cephalosporin with other antibiotics, an association of Cefazolin and Clindamycin was introduced as antibiotic protocol.

### 2.3. Measure phase - dataset description

Data necessary for the study were extracted from the medical records of the University Hospital of Naples Federico II. The data concerning Ceftriaxone have been collected since 2010, and those regarding the new antibiotic Cefazolin plus Clindamycin have been collected since 2011. In particular, for each patient, the following data were collected and categorized (Table 1): gender and age; oral hygiene; ASA score; admission diagnosis; prehospitalization; date of admission; date of surgery and date of discharge; presence of cardiovascular diseases, and diabetes; surgical procedure; post-surgery complications: flap; lymphadenectomy; tracheotomy; infections; dehiscence; fistulae and evolution of the disease.

**Table 1.** Categorization of all the variables analyses in the statistical analyses and modelling.

Variables	Categories
Age	<ul style="list-style-type: none"> <li>• Less or equal to 50 years</li> <li>• In the range (51, 60)</li> <li>• Higher than 60</li> </ul>
ASA score	<ul style="list-style-type: none"> <li>• High: if greater then III</li> <li>• Low: if <math>I \leq \text{score} \leq III</math></li> </ul>
Surgical procedure	<ul style="list-style-type: none"> <li>• Removal</li> <li>• Removal and reconstruction</li> </ul>
Oral hygiene	<ul style="list-style-type: none"> <li>• High</li> <li>• Low</li> </ul>
All the other variables	<ul style="list-style-type: none"> <li>• Yes: if present</li> <li>• No: if absent.</li> </ul>

Lymphadenectomy and tracheotomy are surgical procedures depending on various clinical factors; however, they are more prone to complications since they represent possible entry points for bacteria. Indeed, regarding lymphadenectomy, depending on the tumour stage and the lymph nodes involvement,

neck dissection may be considered, which consists of the removal of lymph nodal stations of the neck because of the risk of metastatic evolution. On the other hand, in case of big tissue removal, it is often observed an increase of edema, hematoma and haemorrhage with the risk of respiratory obstruction. In this condition, unfortunately, tracheotomy becomes strictly necessary. For this reason, in this work, in this work, both lymphadenectomy and tracheotomy are considered as complications rather than surgical procedures. Inclusion and exclusion criteria are shown in Table 2.

The initial dataset was composed by a sample of 125 patients treated with the antibiotic Ceftriaxone and 74 patients treated with the antibiotic Cefazolin plus Clindamycin. After applying the inclusion and exclusion criteria, the dataset was reduced to 66 patients treated with Ceftriaxone and 55 patients treated with Cefazolin plus Clindamycin.

**Table 2.** Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
All patients without exclusion due to medical history (gender, age, presence of cardiovascular diseases and diabetes, oral hygiene).	Patients with allergies to antibiotics.
Patients who have some complication (lymphadenectomy; tracheotomy; infections, dehiscence and fistulae).	Patients with antibiotic shift.
Patients with postoperative LOS $\geq 2$ (which means: day surgery excluded).	

#### 2.4. Analyse phase - statistical analysis

In order to evaluate the effects of treatment on the LOS of the groups of patients, based on the defined category, a statistical analysis was carried out. A normality test of Shapiro Wilk (with a significance level  $\alpha$  of 0.05), attested that data were not normally distributed; therefore, a Mann-Whitney test was applied to all the dichotomous groups, while a Kruskal- Wallis test was applied only on age, since it was divided into three groups. Also in this case, an  $\alpha$  value of 0.05 is used as cut-off value for statistically significance. In Table 3, the variables, the category influencing the LOS and the p-value for the Ceftriaxone treatment are reported.

A statistical significance can be found for some variables (*p*-value shown in bold format); for Ceftriaxone, diabetes, lymphadenectomy or tracheotomy, infections or dehiscence had a major influence on LOS. We recall that lymphadenectomy, due to the large cutaneous access to the neck, requires careful drainage from the surgical site due to the big amount of fluid and blood that is collected in the postoperative period. Indeed, in the presence of lymphadenectomy, a statistically significant increase in hospitalization times is expected, due to the different management that requires this kind of procedure. The presence of drainage, the possible presence of fluid collections and/or hematomas/haemorrhages, possible surgical site infections and the size of surgical wounds require greater attention, treatment and, consequently, a longer duration of hospital therapy. Tracheotomy management involves a period of total isolation of the lower airways until healing of surgical wounds in the oral cavity and a gradual recovery of patient physiological breathing through the upper airways. Once patient normal breathing is restored, the tracheostomy tube is removed, and its access is closed.



Moreover, tracheotomy can lead to the development of nosocomial pulmonary infections due to the direct communication of the lower airways with the external environment. Finally, surgical site post-operative infections are one of the main complications that affect hospitalization time. This postoperative management inevitably influences the LOS, as it is necessary to discharge the patient without any kind of risk, as hematomas, that can affect general health status and the good healing of surgical sites. Furthermore, from Table 3 it emerges that gender, age, ASA score, oral hygiene, cardiovascular diseases, surgical procedure, presence of flap and fistulae do not seem to affect LOS in patients treated with Ceftriaxone.

**Table 3.** Variables influencing LOS for Ceftriaxone.

Variable	Category	N	p-value
Gender	Man	35	0.056
	Women	31	
Age	Age < 51	14	0.074
	50 < Age < 61	14	
	Age > 60	38	
ASA score	Low	38	0.077
	High	28	
Oral hygiene	Low	48	0.349
	High	18	
Diabetes	No	60	<b>0.031</b>
	Yes	6	
Cardiovascular disease	No	33	0.525
	Yes	33	
Surgical Procedure	Removal	55	0.433
	Removal and reconstruction	11	
Flap	No	54	0.326
	Yes	12	
Lymphadenectomy	No	49	<b>0.001</b>
	Yes	17	
Tracheotomy	No	55	<b>0.001</b>
	Yes	11	
Infections	No	61	<b>0.002</b>
	Yes	5	
Dehiscence	No	62	<b>0.002</b>
	Yes	4	
Fistulae	No	65	0.788
	Yes	1	

This kind of analysis is preliminary to the regression one because it allows to understand which variables could be the most important for patients assuming Ceftriaxone, which was, according to the timeline, the former antibiotic used in the hospital department.

### *2.5. Improve phase - introduction of the new antibiotic*

While in the define phase, we clarified the aims of the project, in the measure phase we collected the data and in the analyse phase we focused on understanding the influence of the variables on LOS, the improve phase is not the classical one. Indeed, it coincides with the administration of the second drug (Cefazolin and Clindamycin) while, finally, the control phase corresponds to the statistical analyses.

For testing the capability of the antibiotics in reducing the LOS, several different populations of bacteria were isolated, including *Staphylococcus Spp* and Gram-negative bacteria [43], through the analysis conducted on surgical wounds of patients operated for oral cancer. Since most of cephalosporins, all the available quinolones, and aminoglycosides are in-active against anaerobic bacteria, alternative drugs or drug combinations should be considered. Therefore, in 2011, according to hospital guidelines and the evidence in literature of the success of an association of a first/second generation cephalosporin with other antibiotics, an association of Cefazolin and Clindamycin was introduced as antibiotic protocol [44]. Prophylaxis with Cefazolin plus Clindamycin seemed to be particularly effective because of the absence of postoperative infections. This regimen also appeared to be safe, because no side effects were recorded, and might be considered in patients for whom infection would have critical consequences. This choice was driven by the action of the Cefazolin on the main Gram-positive bacteria such as *Staphylococcus Aureus* Metycillin-Sensible colonizing oral cavity associated to Clindamycin activity on anaerobic Gram-negative flora. As well, Clindamycin is a lincosamide antibiotic used also in patients that are allergic to penicillin or that present infections due to resistant bacteria, such as *Staphylococcus Aureus* Metycillin Resistant. Clindamycin is active also on aerobic Gram-positive cocci, while it is generally resistant to aerobic Gram-negative bacteria, such as *Pseudomonas* and *Legionella*. Clindamycin has been exploited to prevent anaerobic infections including dental and first respiratory tract infections.

## **3. Results**

In this section, the comparison between the two antibiotics is performed (control phase) and the multiple linear regression model is illustrated and discussed.

### *3.1. Control phase - statistical analysis for Cefazolin plus Clindamycin*

Similarly, to what done for Ceftriaxone, the effects of the variables on the LOS of patients undergoing therapy with Cefazolin plus Clindamycin were statistically evaluated based on the same grouping criteria and with the same statistical methods used in the previous case.

In Table 4, the variables and their category influencing LOS for Cefazolin plus Clindamycin are reported; the *p*-value indicates a statistical significance only for some variables (in bold format).

**Table 4.** Variables influencing LOS for Cefazolin plus Clindamycin.

Variable	Category	N	p-value
Gender	Man	27	0.853
	Women	28	
Age	< 51	12	0.172
	50 < Age < 61	16	
	> 60	27	
ASA score	Low	17	<b>0.009</b>
	High	38	
Oral hygiene	Low	42	0.177
	High	13	
Diabetes	No	49	0.082
	Yes	6	
Cardiovascular disease	No	30	0.115
	Yes	25	
Surgical Procedure	Removal	35	0.161
	Removal and reconstruction	20	
Flap	No	36	0.279
	Yes	19	
Lymphadenectomy	No	24	<b>0.004</b>
	Yes	31	
Tracheotomy	No	39	0.207
	Yes	16	
Infections	No	51	<b>0.005</b>
	Yes	4	
Dehiscence	No	48	0,326
	Yes	7	
Fistulae	No	52	0,821
	Yes	3	

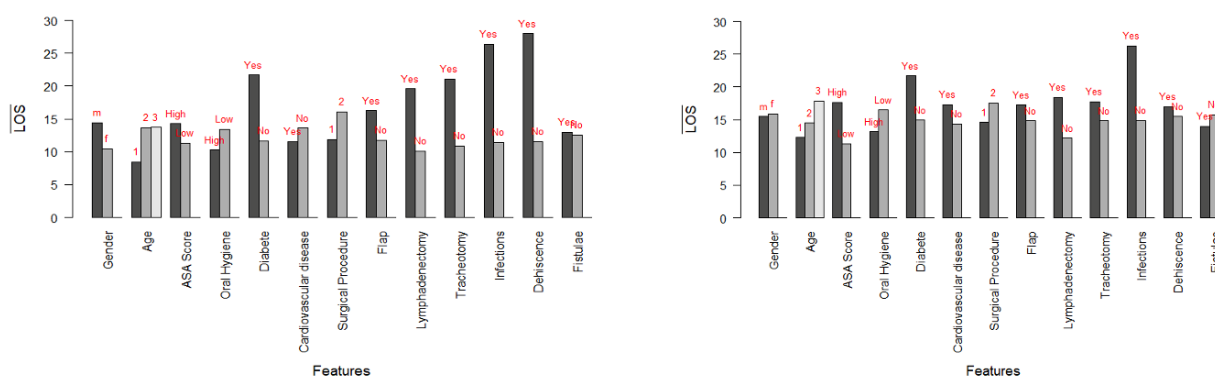
Table 4 shows that LOS, for patients treated with Cefazolin and Clindamycin, is not influenced by the gender and the age. In the same way, oral hygiene, diabetes and cardiovascular diseases do not influence the LOS when these antibiotics are adopted. Instead, infection, lymphadenectomy and high ASA score seem to increase LOS. We recall that the anaesthesiologic evaluation by ASA score is used to determine the anaesthesiologic risk during surgeries. High ASA score (ASA 3–4) is generally conferred to those patients with important associated pathologies, that influence general status and predispose to an increased risk of complications. Indeed, patients with high ASA score are generally old people with other pathologies that sometimes emerge and need to be treated during hospitalization.

As already explained and shown in Table 3, also surgical site infections increase hospitalization times.

This kind of analysis, as well as the previous one for Ceftriaxone, is preliminary in view of the regression model because it allows to understand which variables could be the most important according to Cefazolin plus Clindamycin, which was, according to the timeline, the latter antibiotic used in the hospital department.

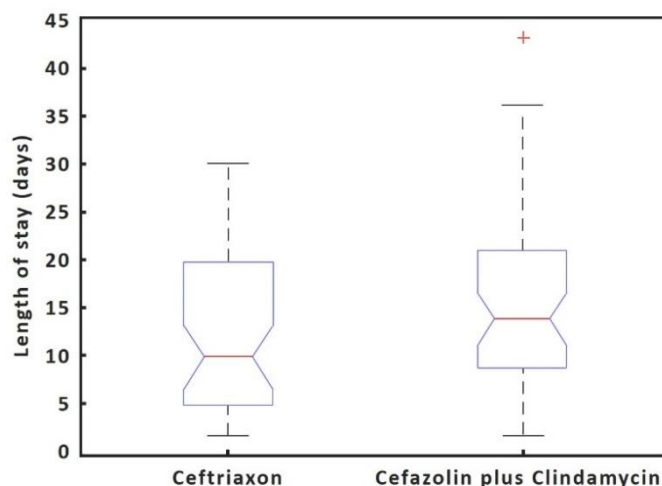
### 3.2. Control phase - comparison between the two antibiotics

In Figures 3 and 4, the mean postoperative LOS of patients for both antibiotics is shown according to each variable. Descriptive statistics for the independent variables, according to the dependent one (postoperative LOS), were carried out.



**Figure 3.** Bar plots of the mean LOS for patients treated with Ceftriaxone (left) and Cefazolin plus Clindamycin (right).

The results for Ceftriaxone were an average of 12.56 days, and a standard deviation of 8.9, while the results for Cefazolin plus Clindamycin were, respectively, a mean of 15.67 days, and a standard deviation of 8.4 days. The boxplot in Figure 4 shows graphically the overall difference in LOS between the two groups.



**Figure 4.** Boxplot of LOS for the two groups.

Table 5 below provides the results of the statistical analysis and the LOS values related to each variable and for both antibiotics; as before, dichotomous groups were analysed with a Mann-Whitney test, while age, which has more than 2 categories, was analysed by a Kruskal-Wallis test.

**Table 5.** Statistical analysis of LOS related to each variable and category.

Variables	Category	Ceftriaxone median [days]	Cefazolin plus Clindamycin median [days]	Relative Difference [%]	<i>p</i> -value
All patients		10	14	28.6	<b>0.028</b>
Gender	Man	12	14	14.3	0.727
	Women	9	14.50	37.9	<b>0.003</b>
Age	< 51	4.5	12	62.5	0.099
	50 < Age < 61	11	14	21.4	0.588
	> 60	11.5	17	32.4	0.089
ASA score	Low	8	9	11.1	0.488
	High	12	17	29.4	0.099
Oral hygiene	Low	10	16	37.5	0.081
	High	9.5	13	26.9	0.258
Diabetes	No	10	14	28.6	<b>0.016</b>
	Yes	25.5	21	21.4	0.818
Cardiovascular disease	No	10	13.5	25.9	0.715
	Yes	10	15	33.3	<b>0.007</b>
Surgical Procedure	Removal	10	12	16.7	0.119
	Removal and reconstruction	20	16	25.0	0.792
Flap	No	10	12.5	20.0	0.080
	Yes	19	15	26.7	0.984
Lymphadenectomy	No	9	9	0	NA
	Yes	21	17	23.5	0.456
Tracheotomy	No	9	12	25.0	<b>0.015</b>
	Yes	21	16	31.2	0.195
Infections	No	10	14	28.6	<b>0.014</b>
	Yes	23	24	4.2	1.000
Dehiscence	No	10	14	28.6	<b>0.014</b>
	Yes	25.5	18	41.7	<b>0.006</b>
Fistulae	No	10	14.5	31.0	<b>0.029</b>
	Yes	NA	14	NA	NA

First, it is worth pointing out that data reported in Table 5 confirm the analysis whose results are

shown in Tables 3 and 4. For instance, from Table 3 (Ceftriaxone), it turns out that diabetes has a significant statistical impact on LOS; indeed, from Table 5, it is clear the strong difference in LOS, 10 vs 25.5, for the absence and presence of diabetes, respectively. Conversely, Table 4 shows that the same parameter has less influence on the LOS for Cefazolin plus Clindamycin; this is confirmed by Table 5, where the difference in LOS is less evident, namely 14 vs 21. Similar observations can be repeated for the other parameters in Tables 3 and 4, where small values of the  $p$ -value have been found. Moreover, Table 5 provides us some complementary information with respect to Tables 3 and 4 since it performs a straight comparison between the performances of the two antibiotics in terms of LOS. First of all, it is worth highlighting that the test on all patients showed that there is a statistically significant difference in LOS between patients who were treated with Ceftriaxone and those treated with Cefazolin plus Clindamycin ( $p$ -value = 0.028).

As regards the test carried out on the different analysed categories, in many cases, except only 6 out of 26, there is a difference in LOS in favour of Ceftriaxone, and in 32% cases this difference is statistically significant. In particular, there was statistically significant difference in favour of Ceftriaxone in women, patients without diabetes, tracheotomies, infections or fistulae, with cardiovascular disease, and patients with or without dehiscence. The biggest difference in terms of percentage between medians, verified through nonparametric tests, was obtained by the youngest patients (-62.5% for those younger than 51 years). Furthermore, it is possible to observe that there were some patients who experienced an increase of LOS with Ceftriaxone: those with diabetes, flap, lymphadenectomy, tracheotomy or dehiscence (the only significant one), those who had a surgical procedure of removal and reconstruction. In particular, there is an increase of time of hospitalization for patients treated with Ceftriaxone that presented diabetes (+21.4%), evidence of dehiscences (+41.7%), underwent surgeries that need reconstruction (+25%), and tracheotomy (+31%). Both good and bad oral hygiene seem to influence LOS in patients treated with Cefazolin and Clindamycin in reason of the +26.9% and +28.9% with respect to patients treated with Ceftriaxone but not in a way statistically significant. Analysing LOS with respect to patients that experienced infections, it seems there is not a statistically significant difference between the two groups, meaning that infections in both groups determine almost the same mean LOS.

Finally, a demographic study of the analysed population was conducted through a chi-square test whose results are shown in Table 6.

Variables ASA score, surgical procedure, flap and lymphadenectomy, showed a statistical significance in sample size. Nevertheless, in almost all these cases the statistical non-uniformity does not affect the results above discussed (see Tables 3 and 4), since they have not a significant impact on LOS for both antibiotics.

**Table 6.** Demographic study through chi square test.

Variables	Category	Ceftriaxone [N]	Cefazolin plus Clindamycin [N]	p-value
Gender	Man	35	27	0.666
	Women	31	28	
Age	< 51	14	12	0.560
	50 < Age < 61	14	16	
	> 60	38	27	
ASA score	Low	38	17	<b>0.003</b>
	High	28	38	
Oral hygiene	Low	48	42	0.648
	High	18	13	
Diabetes	No	60	49	0.739
	Yes	6	6	
Cardiovascular disease	No	33	30	0.618
	Yes	33	25	
Surgical Procedure	Removal	55	35	<b>0.013</b>
	Removal and reconstruction	11	20	
Flap	No	54	36	<b>0.040</b>
	Yes	12	19	
Lymphadenectomy	No	49	24	<b>0.001</b>
	Yes	17	31	
Tracheotomy	No	55	39	0.102
	Yes	11	16	
Infections	No	61	51	0.950
	Yes	5	4	
Dehiscence	No	62	48	0.204
	Yes	4	7	
Fistulae	No	65	52	0.227
	Yes	1	3	

### 3.3. Combining SS and modelling

After SS DMAIC provided the variables involved in the process that have the greatest influence on the LOS, the modelling phase, which can be considered complementary to SS, aimed to implement a Multiple Regression (MR) model, which is an extension of the simple regression model and is

represented by the following Eq (1) [45]:

$$y = \beta_1x_1 + \beta_2x_2 + \beta_3x_3 + \beta_4x_4 + \beta_5x_5 + \beta_6x_6 + \beta_7x_7 + \beta_8x_8 + \varepsilon \quad (1)$$

where  $y$  represents the LOS,  $x_i$  the  $i$ -th independent variable,  $\beta_i$  the  $i$ -th regression coefficient and  $\varepsilon$  the error.

Here, the MR model was derived using the blockwise method of variable selection. The critical  $p$ -value to state a statistically significant difference was set at 0.05. The statistical software IBM SPSS 20 was used to model the data according to the MR.

The MR model was estimated to understand how much the changes in the LOS, considered as the dependent variable, are determined by the analysed factors (*Gender; Age; ASA score; Oral hygiene; Diabetes; Cardiovascular disease; Surgical Procedure; Flap; Lymphadenectomy; Tracheotomy; Infections; Dehiscence; Fistulae*), which are considered as the independent variables or predictors of the MR, and with the idea of predicting LOS by knowing the patient profile for both the antibiotic protocols, i.e. for patients treated with Ceftriaxone and for those ones treated with Cefazolin plus Clyndamicin. Therefore, one model is obtained for each antibiotic and the results are then compared. The MR analyses have been conducted separately because we would be able to predict the final LOS of each patient in advance by starting from his/her clinical characteristics in order to analyse the impact on the hospital organization for each antibiotic. Indeed, as previously mentioned, this is one of the aspects that an HTA study should analyse. Among the independent variables, Surgical procedure, Flap and Fistulae are removed from the model since they showed, for both antibiotics (see Table 3 and 4), a very weak influence on the LOS (very high  $p$ -values). Gender and Age are also removed in order to build a model relying only on clinical/health factors.

Prior to estimating the coefficient of the MR model, as part of the preprocessing step, we assessed the basic assumptions of the MR model (i.e., linearity, independence of the residuals, collinearity, absence of outliers, and homoscedasticity) for both the collected datasets, as summarized in Table 7.

**Table 7.** Assumptions, descriptions and references to supplementary material for the multiple linear regression.

Assumption	Description	Reference to Supplementary Material
Linearity	verify if a linear relationship exists between the dependent variable and each predictors of the model	Figures S1 and S2
Independence of Residuals	verify if the errors of the model are independent	Tables S1
Collinearity	verify if the predictors are not linearly correlated with each other's	Table S2
Outliers	verify if there are influential cases biasing the model	Figure S3
Normality of the Residuals	verify if the errors of the model are normally distributed	Figure S4
Homoscedasticity	verify if the variance of the errors of the model is constant	Figure S5



It is worth mentioning that, in the preprocessing step, the outliers in both the datasets have been identified and properly removed. All the details regarding the preprocessing step and MR's assumptions check are reported in the Supplementary Material.

Table 8 shows the regression coefficients and errors for each predictor obtained with the MR.

**Table 8.** Mean, error and statistical significance of the regression coefficients of the MR model.

Variables	Unstandardized regression coefficients (Ceftriaxone)			Unstandardized regression coefficients (Cefazolin plus Clyndamicin)		
	mean	error	p-value	mean	error	p-value
ASA Score	1.97	0.51	<b>0.000</b>	3.86	0.75	<b>0.000</b>
Oral hygiene	1.50	0.41	<b>0.001</b>	-0.36	0.63	0.575
Diabetes	15.8	2.98	<b>0.000</b>	7.78	2.88	<b>0.010</b>
Cardiovascular disease	0.30	1.46	0.838	1.77	1.61	0.279
Lymphadenectomy	2.38	2.07	0.256	4.04	1.98	<b>0.047</b>
Tracheotomy	7.68	2.79	<b>0.008</b>	0.96	2.37	0.687
Infections	1.03	6.61	0.877	11.13	3.00	<b>0.001</b>
Dehiscence	7.74	6.99	0.273	1.03	2.67	0.703

As from Table 8, the case of Ceftriaxone shows a significant effect of ASA Score, Oral hygiene, Diabetes, and Tracheotomy (reported in bold within the table) on the hospital stay. Instead, the case of Cefazolin plus Clyndamicin shows a significant effect on the LOS for the following variables: ASA Score, Diabetes, Lymphadenectomy, and Infections. Comparing the two regression models, it can be noted that: (i) the ASA Score is confirmed to be the most significant LOS predictor for both the antibiotics; (ii) Diabetes is another predictor that is statistically significant in both the regression models.

Correlation coefficient (R), determination coefficient ( $R^2$ ) and error of each MR model are summarized in Table 9.

**Table 9.** Correlation (R), determination coefficient ( $R^2$ ) and error of the MR model.

	Ceftriaxone	Cefazolin plus Clyndamicin
R	0.92	0.95
$R^2$	0.88	0.90
Error	5.93	5.63

Table 9 indicates that the two proposed MR models exhibit a high predictability. Indeed, the Ceftriaxone model shows an  $R^2$  equal to 0.86 and the Cefazolin plus Clyndamicin shows an  $R^2$  equal to 0.90. Therefore, it can be concluded that for both antibiotics, approximately 85–90 percent of the variance in the LOS can be explained by the selected patients' clinical characteristics. The authors are aware that the predictors included in both models could not be the only variables affecting the overall LOS. Nevertheless, the obtained results suggest that the included factors explain an important role played by the variance in the LOS. In addition, it is worth mentioning that the chosen independent

variables are readily available in the patients' clinical record and history, thereby allowing a lean data collection and management process.

#### 4. Discussion and conclusions

It is known that a proper HTA approach improves health environment management thanks to a more efficient use of data and a depth evaluation of sanitary needs, making it possible to better understand technologies features, their health effects and organizational impact. In general, the HTA is mainly related to the purchase of medical devices or technologies [33]. The HTA studies related to drugs mainly involve arrangement for reimbursement [34]; there exist some studies concerning drugs administration, however, to date, a correct antibiotic prophylactic protocol to prevent a long hospitalisation in oral cancer surgery is not clearly defined. To this regard, the rationale, on which our approach is based, is that the specific need of the hospital was the evaluation of the impact of the antibiotics on the management issues; therefore, in this study, we compared two drugs by HTA approach, which is not common in the literature. Furthermore, the use of SS DMAIC methodology, as a tool of HTA, has rarely been used in literature. More specifically, this paper relies on the use of the SS methodology with the DMAIC cycle to handle a healthcare issue regarding the comparison of two antibiotics in the oncology field.

SS through DMAIC cycle provides researchers with a well-structured problem-solving tool that is useful for a wide range of analysis, as testified by other studies [13,19]. In this case, the comparison between the two antibiotics was carried out by using the LOS as CTQ, taking into account variables such as the kind of surgery and comorbidities (infections, dehiscence, flap, etc.). We choose the LOS as CTQ because it is widely recognized as an indicator of inpatient care inefficiency [46]. Indeed, a predictive model of LOS can serve as a powerful decision-making tool for many purposes, such as:

- evaluating performance of both the medical staff and the hospital;
- providing feedback to the patients and/or their relatives at the time of admission;
- planning the continuity of care by scheduling the activity and managing resources according to the predicted LOS;
- developing admission policy models by knowing in advance the number of available beds for future days, as also showed in other works [47].

Regarding the choice of the drugs to be compared, as already mentioned, Ceftriaxone is a third-generation cephalosporin antibiotic belonging to beta lactam family. In clinical practice, it is generally used to treat most of infections sustained by antibiotic resistant bacteria. It is active on Gram positive bacteria with a tropism to skin and soft tissues infection. Because of the increasing risk of resistance to bacteria of this drug, Ceftriaxone should not be used as first choice and without a certified susceptibility from the bacteria, except when an empiric antibiotic therapy is required in case of sepsis. Postoperative complications such as dehiscence or fistulae are often related to antibiotic resistant bacteria. To specifically individuate responsible bacteria of infectious complications, additional exams that inevitably increases the length of hospitalization are generally required. This is evident when some of these oncological patients need an immediate postoperative period of intensive care. Contacts between oncological patients, that are often immune deficient, with other patients, belonging to other departments hosted in the intensive care unit, may determine the development of infections. Not only infectious complications can affect the healing of surgical sites, but they also affect the general health status of patients. It is impossible to discharge a patient without ensuring safe conditions.

That said, the results obtained, under the guidance of DMAIC, show, with a statistical significance, that patients treated with Ceftriaxone experienced in many cases a lower LOS. Nevertheless, depending on the surgical procedure, an increase of postoperative stay is observed in those patients that were treated with Ceftriaxone and that needed a reconstructive surgery and/or neck dissection, tracheotomy and the use of a flap for the reconstruction. In addition, the obtained results show that the group of patients treated with Cefazolin and Clindamycin present on average an increase of LOS in all patients. It is particularly evident in patients with a high ASA score, a low oral hygiene, or cardiovascular associated pathologies. Patients undergoing simple exportation without neck dissection and/or tracheotomy seem to experiment an increased time of postoperative stay when treated with Cefazolin plus Clindamycin. Furthermore, we implemented a modelling phase (within the control phase of the DMAIC cycle) that has allowed us to achieve more insights about the antibiotic performance, which, apart from confirming the statistical analysis results, can give physicians additional useful information. Indeed, such model can highlight which variables are more sensible to the drug under analysis. Of note, the  $R^2$  between 0.85 and 0.91, achieved respectively for the two treatments, can be considered good results in the biomedical engineering area, thus representing robust models which clinicians can rely on.

We can conclude that, with the aid of the proposed methodology, it is possible to support the analysis of the impact that two antibiotics have on the LOS, thereby offering the opportunity to guide and help the clinical decision-making process. The novel contributions, brought by this study, concern different issues. First, we propose a new perspective for the HTA application where the effect of two treatments on the organizational and managerial dimensions of the healthcare structure is analysed. Secondly, we integrate the SS DMAIC cycle in the assessment process, thereby suggesting a potentially novel methodology in the framework of HTA evaluations. Thirdly, we added a further tool to the DMAIC approach, i.e., the introduction of a regression model preceded by a data preprocessing step, in order to deepen the traditional statistical analysis, and offer a more advanced tool for making projections and further observations by taking into account all the variables of the process as a whole. Finally, it is worth underlining that our study provides a systematic procedure, which combines different and well-assessed methodological tools, to serve as a potential guidance in the healthcare decision-making.

### Conflict of interest

The authors have no conflict of interests to declare.

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