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Infections Prevention and Control in caesarean section: multifacet analysis of determinants of rational use of antibiotics in Benin.

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Abbreviations

Abbreviations	Definitions
ABRP	Agence Béninoise de Régulation Pharmaceutique
AMR	Anti-Microbial Resistance
ANCQ	Angence Nationale de Contrôle de Qualité des produits de santé et de l'eau
ANPS	Agence Nationale de Protection Sanitaire
ARES	Académie de l'Enseignement Supérieur
CAI	Conseil de l'Action Internatioanle
CPG	Clinical Practice Guidelines
CS	Caesarean Section
ESBL	Extended-Spectrum Beta-Lactamase
FCFA	France de la Communauté Financière d'Afrique
GAP-AMR:	Global Action Plan on Antimicrobial Resistance
HAIs	Healthcare-Associated Infections
IPC	Infection Prevention and Control
MRSA	Methicillin-Resistant Staphylococcus aureus
MUST PIC	MUltidisciplinary Strategy for Prevention and Infection Control
SDGs	Sustainable Development Goals
$	Dollar
WHO	World Health Organisation

INTRODUCTION

Introduction

Infection Prevention and Control (IPC) is a practical, evidence-based approach which prevents patients and health workers from being harmed by avoidable infection and, in addition, prevents antimicrobial resistance [1]. Preventing harm to patients, health workers and visitors due to infection in health care facilities is fundamental to achieving quality care, patient safety, health security, and the reduction of antimicrobial resistance (AMR) and healthcare-associated infections (HAIs) [2].

HAIs are infections occurring in a patient during the process of care in a hospital or other healthcare facility that were not manifest or incubating at the time of admission [3]. HAIs represent the most frequent adverse event during care delivery and constitute an enormous burden since each year, hundreds of millions of patients around the world are affected by HAIs [3], [4]. Most HAIs (urinary tract infection, pneumonia, surgical site infection, endometritis, and sepsis) can affect patients with great consequences on personal and global levels such as longer hospital stays, economic burden (lost wages sometimes), psychological impact, and death [5]. Even if data on HAIs are scarce in Africa, reviews reported a high rate in comparison to developing countries. The first review based on the data from 1995 to 2008, reported a rate of 15.5%, and in the second that pooled data from 10 countries (1995 to 2009), the overall prevalence of HAIs ranged from 2.5% to 14.8% [4], [6] versus 7.1% in European countries [7]. A study performed in Burkina Faso in 2011 showed a prevalence of 71.8% of HAIs [8], and 14.3% from a

point-prevalence survey in Nigeria in 2019 [9]. In Benin, a nationwide survey in 2012 reported 19.1% of nosocomial infections [10].

AMR occurs when microorganisms change over time and no longer respond to antimicrobials making infections more difficult to treat and increasing the risk of disease spread, severe illness, and death. According to the World Health Organization (WHO), the AMR is one of the top 10 global public health threats and requires multisectoral action to achieve most of the Sustainable Development Goals (SDGs) [11].

The misuse (use when it is not needed), overuse (use more often than necessary), and underuse (use less than is required) of antimicrobials are the main drivers in the development of drug-resistant pathogens [11], [12]. The cost of AMR is a burden on the patient level (10 million deaths by 2050, with 4 million in African countries), and on the healthcare level ($300 billion to more than $1 trillion annually by 2050) [13]. The consequences of AMR are numerous such as prolonged illness resulting in longer hospital stays the need for more expensive antimicrobials, other financial challenges, disability, and death [11]. Data in African countries reported increasing rates of AMR as well community-acquired as multidrug-resistant pathogens from healthcare facilities [14]. In this review of 2013, Extended-spectrum beta-lactamase (ESBL) production has been reported in 4-46% of Enterobacteriaceae with high rate co-resistant to ciprofloxacin, gentamicin, and cotrimoxazole, and methicillin-resistant Staphylococcus aureus (MRSA) isolated in clinical samples, prevalence was from 12.5% to

29.6% [14]. A 2014 study in Nigeria reported the sensitivity of pathogens isolated from surgical wounds infections as follows: above 98% of resistance to Bêta-lactam antibiotics and more than 70% of resistance to erythromycin, fusidic acid and tobramycin [15]. In a Benin study published in 2015, ESBL was isolated in 35.5% of biological samples with high resistance to amoxicillin (92.8%), ampicillin (94%) and cotrimoxazole (85.7%) [16]. In the MUST-PIC study, in 2020, ESBL producers were represented by 69.4% of *Escherichia coli*, 83.3% of *Klebsiella pneumoniae* and 65.3% of staphylococcus were MRSA. The high rates of multidrug resistance were reported for numerous classes of antimicrobials such as aminoglycosides (67.8%), fluoroquinolones (85.7%), and cotrimoxazole (67.8%) [17]. This situation is a great concern since the range of antimicrobials available in African countries is limited [14].

Although most physicians are aware of the concern of AMR, a great part of them still underestimate this problem in their hospitals and inappropriately prescribe antibiotics [18]. At the hospital level, AMR can be tackled by enhancing Infection Prevention and Control, controlling the source of infection when it is needed, prescribing antibiotics only when they are truly required, prescribing appropriate antibiotic(s) with adequate dosage to treat the infections, using the shortest duration of antibiotics based on evidence of guidelines, educating the communities in which we work about the need to use antibiotics wisely [19]. To reach this goal, the availability of data on HAIs, AMR, and antibiotic consumption at the hospital and national levels are essential for the

development of guidelines for appropriate clinical practices and antibiotic use. On the one hand in high-income countries, where data on HAIs, AMR, and antibiotics consumption are available and numerous clinical guidelines are developed. Despite this, healthcare professionals' adherence is reported to be low [20], [21]. On the other hand, in low-income countries, the rate of HAIs, and AMR from sparse data are high [4], [22], [23], and antibiotics consumption is less known and guidelines are lacking [14]. For example, in Benin, despite the increasing rates of HAIs and AMR (as reported above), the antibiotics consumption is less documented. In 2008, a study assessing antibiotic prescriptions for outpatients in Cotonou reported that 70.6% of prescriptions were inappropriate [24], and a high rate of self-medication with antibiotics, 40.8% was reported in a nationwide survey in 2012 [10]. This high rate of self-medication with antibiotics is due to the possibility in people have in Benin to buy antibiotics without medical prescription.

In 2014, Baxerres *et al.* in an anthropologic study performed in Benin indicated that this situation originated after the colonial era when the African States could not continue to provide free medicines and health services to people. From the 1980s onwards, the commercial nature of medicines was introduced in the African countries with degeneration of the situation after the Bamako Initiative (1987) where user fees were effective in healthcare. This initiative was a formal statement adopted by health ministries of African countries in Bamako (Mali). The aim was to implement strategies designed to increase the availability of essential drugs

and other healthcare services in Sub-saharian African countries [25]. According to Hardon, the Bamako Initiative intended to solve the problems in the financing of primary healthcare due to the severe economic crises facing Sub-Saharan Africa [26]. Since then, people have sought means to treat diseases as cheaply as possible. It results in the development of the informal circuit of medicine (market, street shops), and an out-of-supervision distribution of medicines including antibiotics in healthcare facilities such as pharmacies [27]. In 2017, the government of Benin was committed to fighting against the informal circuit. In healthcare facilities, on the same impulse, the government through the regulatory agency (Agence Béninoise de Régulation Pharmaceutique, ABRP) makes the call in February 2020 for the rational dispensation of antibiotics in the pharmacies. The next step will be the concretization of the project of the e-pharmacy platform that the government plans to implement for pharmaceutical products' traceability in order to avoid substandard and falsified drugs in the formal system [28].

To reduce the burden of HAIs and AMR worldwide, the WHO often launches global challenges on different components of IPC. Among them, two have a specific link to our thesis. The first Global Patient Safety Challenge, a core program of the World Alliance for Patient Safety was launched in 2005 with the topic "*Clean care is safer care"* [29]. The second Global Patient Safety Challenge entitled *" Safe surgery saves lives*" was launched in 2008 to improve the safety of surgical care around the world [30]. In addition, the WHO endorsed a global action and calls every nation, stakeholders, healthcare workers, and patients to reduce the impact

of AMR and limit its spread [31]. For this end, five strategic objectives have to be reached [19]:

- raising awareness and understanding of antimicrobial resistance,
- reinforcing knowledge through surveillance and research,
- decreasing the incidence of infectious diseases,
- promoting the rational use of antimicrobials,
- increasing investment in new medicines, diagnostic tools, vaccines, and other interventions in all countries.

Those different actions performed are to help nations to be active in IPC. What is challenging is that only a few hospitals in Africa participate in them. For example, only 5 African countries (including Benin) out of 53 included participated in a study of the Global Point Prevalence Survey on antimicrobial consumption and resistance in adult hospitals carried out by Biomerieux in 2015 [32]. It results in a lack of data or updated data in Africa.

Since the WHO reported an increase of infections in surgical care with important risks for patient safety, particular attention has to be paid. In the frame of this thesis, we focused our research on the caesarean section (CS) which is one of the surgical interventions commonly practiced in Benin, and which involves at least two people (the mother and newborn). As in many low-income countries, user fees are one of the barriers to accessing care services. Several sub-Saharan African countries have introduced user fee exemption policies specifically for the caesarean section to remove this barrier. In April 2009, Benin also launched a user fees

exemption policy. In this policy, a kind of guideline for the use of antibiotics (the national free kit) is made available. This kit contains the required materials for the surgical intervention including antibiotics for prophylaxis (ampicillin, gentamicin, and metronidazole in injectable forms), and for post-partum (amoxicillin and metronidazole in tablets) [33]. Indeed, since the launch of this policy, several studies were performed to assess its implementation and explore different stakeholders' opinions, but there is no data about the use of the medicines especially antibiotics in the kit regarding the threat of antimicrobial resistance and the call for rational use of antibiotics worldwide.

In other words, despite international initiatives, there is a lack of actionable data in some countries, including Benin. Without updated valid information about AMR and the use of antibiotics, and without guidelines, practicians are helpless in the face of HAIs. To fill the gap of updated knowledge in Benin, we aimed to provide data on the prevention and control of HAIs and analyze the determinants for promoting the rational use of antibiotics to reduce the occurrence of AMR.

This research was possible thanks to the funding of ou thesis project since 2016 by the Conseil de l'Action Internationale (CAI) of université catholique de Louvain and the multidisciplinary project funded by "l'Académie de l'Enseignement Supérieur" (ARES) which started in 2018. This ARES's research project for development (PRD: Projet de Recherche pour le Developpement) has been set up based on our first data on antibiotic utilization collected in 2016, which highlighted that there were several aspects

of Infection Prevention and Control in the Benin hospitals to investigate with the need for interventions. Thus, the project named "MUltidisciplinary Strategy for Prevention and Infection Control"(MUST-PIC) aimed to reduce HAIs by improving hand hygiene and rational use of antibiotics in six hospitals including the four where we performed our studies. In addition to the present thesis, two theses were realized in digestive and obstetric surgeries to collect data on different topics and implement interventions. Figure 1 displays an overview of the 3 theses.

In the following lines of this introduction, we will focused on three concepts which have link with our thesis such as "Antibiotics utilization and rational use", "Clinical practices guidelines and healthcare professionals' beliefs and knowledge" and "Ceasarean section and user fees exemption policy".

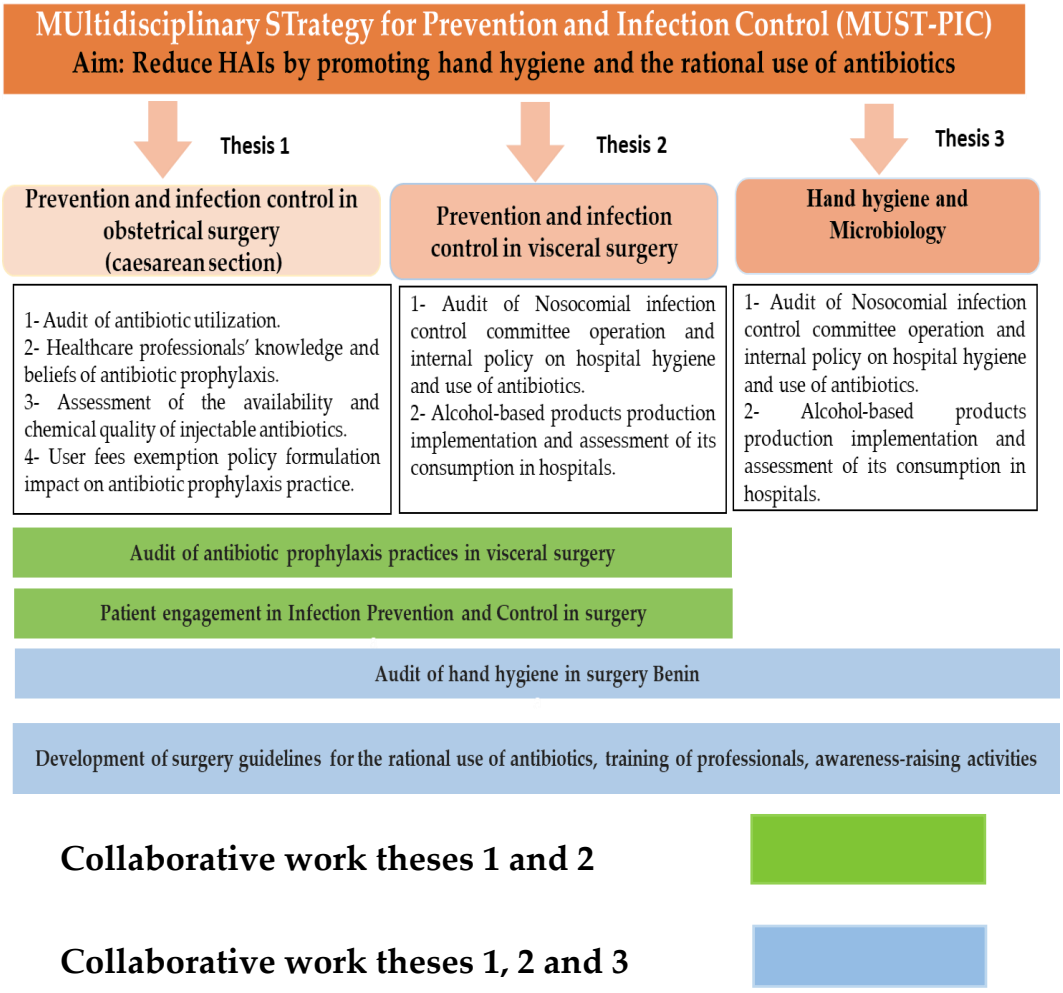

Figure 1: Overview of the 3 theses of the MUSTPIC project

Section 1

Antibiotic usage and rational use

Antibiotics are used to treat and prevent infections. Antibiotic prophylaxis is defined as ***"a brief course of an antimicrobial agent initiated before an operation begins to reduce intraoperative microbial contamination to a level that will not overwhelm host defense and result in infection"*** [34]. The antibiotic prophylaxis in surgery is practiced following the wound classification of Altemeier [35]. This classification is based on the level of risk of infection. Surgical wounds are definied in four classes as describe in the Box.1 below. Caesarean section is a class II wound contamination intervention and antibiotic prophylaxis is indicated [36].

Box.1: Surgical wound classification and antibiotic's use

Classes	Description	Use of antibiotic
Class I	Wounds are considered to be clean. They are uninfected, no inflammation is present, and are primarily closed.	Prophylaxis
Class II	Wounds are considered to be clean-contaminated. These wounds lack unusual contamination. Class 2 wounds enter the respiratory, alimentary, genital, or urinary tracts	Prophylaxis
Class III	Wounds are considered to be contaminated. These are fresh, open wounds that can result from insult to sterile techniques or leakage from the gastrointestinal tract into the wound.	Therapy
Class IV	Wounds are considered to be dirty-infected. These wounds typically result from improperly cared-for traumatic wounds.	Therapy

Maternal morbidity and mortality related to infection were described to be a global concern. Obstetric infections are reported to be the third most common cause of maternal mortality. In low and middle-income countries, this mortality was estimated at 10.7% versus 4.7% in high-income countries [37].

Several factors increase the risk of maternal peripartum infections, including pre-existing maternal conditions (e.g. malnutrition, diabetes, obesity, severe anemia, bacterial vaginosis, and group B streptococcus infections), as well as prolonged prolabor rupture of membranes, multiple vaginal examinations, manual removal of the placenta, operative vaginal birth and caesarean section. As such, the strategies to reduce maternal peripartum infections and their short and long-term complications have been directed at improving infection prevention and control practices. In caesarean section, the most important risk factor for infection is in the immediate postpartum period with a five-fold to 20-fold increased risk compared to vaginal birth [38]. Effective intervention for preventing morbidity and mortality related to maternal infection is the prophylactic and therapeutic use of antibiotics [39]. Antibiotic prophylaxis is recommended in CS to prevent post-operative poor outcomes such as surgical site infections, endometritis, urinary tract infections, and morbidity with economic and psychological impacts [40]–[42]. To be efficient, prophylaxis has to meet the five conventional criteria summarized in the Box.2 bellow [39], [43].

Box.2: Five conventional criteria of antibiotic prophylaxis

- **Indication**: in caesarean section, antibiotic prophylaxis is considered to be essential to reduce post-operative poor outcomes,
- **Choice of antibiotic**: first-generation cephalosporins are the preferred antibiotic class for prophylaxis as part of efforts to contain antimicrobial resistance. Cefazolin is the conventional antibiotic recommended worldwide.
- In the case the recommended antibiotic classes are not available, other classes of antibiotics may also be used. The antibiotic class chosen should be based on local antimicrobial resistance guidance, local bacteriologic patterns of post-caesarean infectious morbidity, safety profile, the physician's experience with that specific class of antibiotics, availability, and cost.
- **Timing of administration**: prophylactic antibiotics are recommended for women undergoing elective or emergency caesarean section and should be given 30–60 minutes before skin incision.
- **Preoperative dose**: double the usual adult dose of an antibiotic is recommended for caesarean section. Any necessary following doses are administered in the usual adult dose. The dose can be increased in obese patients.
- **Duration of prophylaxis**: antibiotic prophylaxis can be administered in single-dose. Other clinical factors (e.g., high maternal body mass index, prolonged labor, prolonged duration of surgery, extensive surgical manipulation, or massive blood loss) might increase the risk of developing post-caesarean infections. In this case, the duration can be prolonged to 24-48 hours.

Several learned societies provided strong recommendations for antibiotic prophylaxis. Some of them are displayed in Table 1 below:

Table 1: Antibiotic prophylaxis recommendation

Society	Recommendations
World Health Organization (WHO, 2021) [39]	Single doses of first-generation cephalosporins or penicillin should be used in preference to other classes of antibiotics.
Society of Obstetrics and Gyneacology of Canada clinical practice Guideline [43]	**1.** All women undergoing elective or emergency Caesarean section should receive antibiotic prophylaxis. (I-A) **2.** The choice of antibiotic for Caesarean section should be a single dose of a first-generation cephalosporin. If the patient has a penicillin allergy, clindamycin or erythromycin can be used. (I-A) **3.** The timing of prophylactic antibiotics for Caesarean section should be 15 to 60 minutes prior to skin incision. No additional doses are recommended. (I-A)
French society of Anesthesia (Société Française d'anesthésie Réanimation, SFAR, 2018), Expert opinion [44]	**1.** Cefazoline 2g IV, single dose **2.** Cefamandole 1.5 g IV, single dose **3.** Cefuroxime 1.5 g IV, single dose **NB**: The choice of antibiotic should include in its spectrum bacteria frequently responsible of surgical site infections (Recommendation Grade 1+)
Benin national kit of caesarean section [33]	**Simple caesarean section** 6 vials of ampicillin 1g, 2 bottles of metronidazole 500mg **Complicated caesarean section** 12 vials of ampicillin 1g, 6 bottles of metronidazole 500 mg, 6 vials of gentamicin 80 mg. **NB**: The regimen of antibiotic prophylaxis depends on each practitioner.

From the data of number of studies around the world, antibiotic prophylaxis in CS intend to prevent post-delivery poor outcomes such as surgical wound infection, endometritis, maternal complicated infections [41], [45]–[47]. Although studies could be performed in variable context, a review of randomized clinical trials regarding recommendations on antibiotic prophylaxis showed its benefits in reducing of post-operative infections [48]. It was concluded that prophylactic antibiotic should be routinely administered to all women undergoing CS. However, as stated in the recommendation of the SFAR (Grade 1+), the choice of the antibiotic has to include the ecology of the bacteria frequently met in surgical site infections. Antibiotic prophylaxis must be directed at a specific bacterial target by using a narrow spectrum antibiotic. Any recommendation of antibiotic for prophylaxis in caesarean section must be based on methodological acceptable study that validate its activity, local distribution and tolerance in this indication [44]. In addition, the timing of administration, the dose administered, and the duration of administration have to meet the conventional criteria to ensure the safety of women and their babies and prevent the evolution of antimicrobial resistance[48]

Antibiotic therapy is used in the occurrence of post-operative infections. The antibiotics recommended depends on local bacterial susceptibility. The WHO provided an updated guideline for an efficient treatment of post-caesarean to ensure the patient quality of life and avoid the occurrence of antimicrobial resistance [49]. The current use of antibiotics in prophylaxis and therapy in the

caesarean section in Benin is documented in our paper included in chapter I of this thesis.

The misuse and overuse of antibiotics are worldwide reported with many consequences on personal and global levels [50]. Actions at all levels of healthcare systems and nations are essential to reduce this threat [31]. Among measures, the rational use of antibiotics is highlighted to be important [51]. The rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their requirements, for an adequate period, and at the lowest cost to them and their community" [29]. It is an essential component of diseases' prevention and treatment. When used inappropriately, medicines can harm or being onerous. In the case of antibiotics, the rational use aims to reduce the impact of antimicrobial resistance, while ensuring access to the best treatment available [19]. To reach this objective, simultaneous training is needed for both doctors and patients [52], [53]. The WHO describes the promotion of rational use of medicines as un process including several steps such as [54]:

- identify the problem and recognize the need for action (quantitative and description studies),
- identify underlying causes and motivating factors (quantitative and qualitative studies),
- list possible interventions,
- assess resources available for action,
- choose an intervention or interventions to test

- monitor the impact and restructure the intervention. (qualitative and qualitative studies)

Indeed, if healthcare professionals are key to the prescription of antibiotics, patients have an important contribution to Infection Prevention and Control. We explored in the framework of this thesis, the extent to which patients can be involved in surgical care in Benin Settings.

The other challenge that low-income countries face in the use of antibiotics is their availability and their quality. Several care facilities are often stocked out of medicines including antibiotics leading to delays in the care initiation. This stock out can be due to procurement financing and processes, poor management of the supply chain, supply capacity, communication, and the state of road infrastructure, distribution resources and planning methods, personnel staffing and training, and coordination among stakeholders [55]. Studies in Mozambique and Sudan reported the non-availability of antibiotics in hospital pharmacies [56], [57]. In addition, the poor quality of antibiotics can fail treatment with death as a consequence, and increase the antimicrobial resistance in the case of the antibiotics [58], [59]. The WHO estimates that 1 in 10 medical products in low-income countries are substandard and falsified medicines, and fewer resources are available to eradicate the threat [60].

Substandard medicines also called “out of specification” are defined as “authorized medical products that fail to meet either their

quality standars or their specifications, or both". Substandard can result in poor manufacturing practices, unsuitable packaging, or inappropriate transport or storage conditions. Whereas falsified medicines or counterfeit medicines are defined as "medical products that deliberately or fraudulently misrepresent their identity, composition, or source [61]. The proportion of substandard and falsified medicines has been estimated at less than 1% in industrialized countries, and 10 to 30% in low incomes countries [58]. Since 2013, 1500 reports of reports of substandard and falsified medecines have been sent to the WHO, and 42% of them were from the African region [61]. In a systematic review, antimalarials (19.1%) and antibiotics (12.4%) are the most concerned medicines [62]. The economic impact of substandard and falsified medicine is ranging from $10 billion to $200 billion worldwide [62]. In Benin, some studies reported poor quality of oral antimalarials [63], [64]. Substandard and falsified medicines are mostly spread in the informal supply chain which is widely frequented by low-income countries population. Several nations work to fight substandard and falsified medicines using differents methods [65]. Consumer (patient)'s education and awareness are essential to limit the use of medicines from informal supply chain in order to reduce their consequences on health. Through a transversal and analytic study, we documented the availability of antibiotics in hospital pharmacies and assessed the quality of injectable antibiotics used in prophylaxis in the studied hospitals.

Section 2

Clinical practices guidelines and healthcare professionals' beliefs and knowledge

Clinical practice guidelines (CPG) are recommendations that guide how to diagnose and treat disease. They are based on a systematic review of the evidence, and the evaluation of the benefits and harms of alternative care options [66]. According to the WHO, the guideline is any document containing recommendations about healthcare intervention whether these are clinical, public health, or policy recommendations [67]. The improvement of quality and consistency of care, than de reduction of morbidity and mortality are some CPG benefits among several [68]. Using clinical guidelines can then help to decrease expenditures in healthcare. At the healthcare professional level, clinical guidelines can improve the quality of clinical decisions. They provide explicit recommendations for healthcare professionals who are uncertain about how to proceed, reverse the beliefs of doctors used to outdated practices, ameliorate the consistency of care, and give authoritative recommendations that reassure practicians about the appropriateness of their treatment policies [68].

The WHO has adopted international recognized standards and methods for guidelines development to ensure that guidelines are free from bias, meet public health needs, and are consistent with the following principles [67]:

- recommendations are based on a comprehensive and objective evaluation of the available evidence,

- the process followed to develop the recommendations is clear and allows the reader to see how a recommendation has been developed, by whom, and on what basis.

Guidelines development is about challenging and long process. Several sources described the steps of the process. Based on the description of the WHO the steps of the process are summarized in **Table 2** [67], [69] .

Table 2: The steps of clinical practices guideline development **(1/2)**

N°	Guideline development steps	Definition of activities
1	Determining the need for and scope of guidelines	The body responsible for developing the guidelines should specify the problem or objective and define what is involved in general terms.
2	Convene a multidisciplinary panel to oversee the development of the guidelines	The panel's precise composition will depend on the nature of the guidelines but should be designed to encourage the expression of diverse interests
3	Define the purpose of and target audience for the guidelines	The panel should clarify the purpose of and target audience for the guidelines.
4	Identify health outcomes	The appropriate outcome measures will differ depending on what is under consideration, e.g.: mortality, morbidity, quality of life, and patient satisfaction…).
5	Review the scientific evidence	A systematic literature review should be undertaken to establish the benefits and harms of the possible interventions.
6	Formulate the guidelines	The guidelines should be constructed based on the best available scientific evidence of the probable outcomes associated with different clinical interventions.

Table 2: The steps of clinical practices guideline development **(2/2)**

N°	Guideline development steps	Definition of activities
7	Formulate a dissemination and implementation strategy	Develop a plan for disseminating and implementing the guidelines targeting all potential users and defining processes that will encourage them to adopt and implement the guidelines.
8	Formulate an evaluation and revision strategy	Specifying short-term and long-term frameworks for evaluation and identifying who will conduct the studies.
9	Produce the guidelines	Presented clearly and concisely as possible; define important terms and others that might be misinterpreted.
10	Report on the guidelines' development process	It should contain a description of the guidelines' development process, the dissemination, implementation, evaluation, revision strategies, and matters for future research.
11	Assess the guidelines document	Clinical applicability, flexibility, reliability and reproducibility, validity, and clarity.
12	Consultation	The guidelines should be referred for examination to a wider group of interested parties that may not have already been involved.

WHO, Handbook for guideline development, 2012.

Over the time that the development of practice guidelines can take, it also requires competencies. The WHO estimates around 10-20 people to be involved and approximately US$ 300,000 to spend for developing guidelines at their level [67]. It appears that it will be unfeasible for low-resource countries to perform their practice guideline, especially in the frame of prevention and infection control where the local ecology is important to be considered. In addition to limited resources, specific competencies are rare. This can explain the rare and poor quality of clinical practice guidelines available [70], [71].

With regard of the occurrence of antimicrobial resistance and the trend of the promotion of quality care in surgery by the WHO, guidelines for antibiotics usage are relevant especially for prophylaxis. As reported previously, several nations and organizations developed guidelines for prophylaxis including for CS such as the WHO [39], [72] and "Société Française d'Anesthésie Réanimation" (SFAR) [44]. In Benin, even if antibiotic prophylaxis is practiced in CS with selected antibiotics or not, any official guideline for antibiotic prophylaxis in CS was not documented.

Despite wide promulgation, clinical practice guidelines have had limited effects on changing physician behavior, and adherence to them is still low in healthcare [73], [74]. A number of barriers to non-adherence to guidelines were described as unfamiliarity, disagreement, low perceived benefit, low self-efficacy, and time constraints [75]. In 2020, Correa et al. described barriers and facilitators in a systematic review according to each context **Table 3** [76]

Table 3. Barriers and facilitators of adherence to guidelines **(1/3)**

Healthcare-related context	Barriers	Facilitators
Political and Social	The absence of a leader establishes priorities and manages the implementation process. Difficulties with teamwork. Lack of coordination and disagreement with colleagues. The absence of recognizing the role of the professional. Lack of clarity of responsibilities. Financial constraints for the adoption of new interventions.	Consistent leadership creates enthusiasm and provides clear objectives of care. Commitment of the multidisciplinary team members and the support of administrators. Exchange of experiences among staff The superiors' support for the implementation of the guide Confidence in other experienced colleagues
Health Organizational system	Lack of time allowed for researching, studying, and implementing the guidelines. Too little time in the medical consultation. Shortage of hospital resources and equipment. Few people in the health area were dedicated to specialized care.	Existence of multidisciplinary teams. Application of technology to improve the practice. The creation of alarms and automatic reminders to implement the recommendations. Efficient organizational processes. Positive attitudes of the health personnel towards change. Multi-professional audit meetings, with feedback and good communication.

Table 3. Barriers and facilitators of adherence to guidelines **(2/3)**

Healthcare-related context	Barriers	Facilitators
Clinical practices guidelines (CPG)	Lack of clarity in the CPGs. Belief that the evidence in the guidelines is incorrect or that the evidence is not sufficient to properly inform. Belief that CPGs are too rigid or that they are in conflict with the practice accepted by healthcare personnel and do not always translate to day-to-day tasks.	Very good information and early education. Peer support and feedback between patients, interest of the patients or motivation to follow the recommendations. Health awareness and an understanding of the consequences of not following the recommendations
Healthcare professional	Ignorance of the existence of the CPGs or recommendations. The basis of evidence and how to search for information. Distrust of one's ability and fear of implementing the guidelines, Fear of harming, or damaging the patient-doctor relationship, inexperience, and distrust of prescriptions. Lack of familiarity with the guideline recommendations	Education about the guidelines, Specific training or educational programs High motivation to implement the intervention Positive attitude Good communication and behavioral change skills of healthcare personnel

Table 3. Barriers and facilitators of adherence to guidelines **(3/3)**

Healthcare-related context	**Barriers**	**Facilitators**
Patient	Unawareness of patients regarding the guideline. Unawareness about the system characteristics and their disease. Negative attitude of the patient toward the guide. Reluctance to follow the recommendations. Expectations in contrast to the opinion of the doctor. Lack of family support. Inadequate patient-doctor relationships. Lack of confidence on the part of the patient.	Very good information and early education. Peer support and feedback between patients, interest of the patients or motivation to follow the recommendations. Health awareness and an understanding of the consequences of not following the recommendations

V.C. Correa et al., Health research Policy and System, 2020

Following the guidelines can reduce the freedom of action of the healthcare professionals and constrain the choices at the expense of possible alternative solutions, eventually still effective and even more beneficial to scientific progress [77]. To avoid this risk, the guidelines have to be updated as defined in the report. Healthcare professionals acquire knowledge in vocational and continuous education. This knowledge is often improved by experience. The adherence to guidelines depends on the level of knowledge and the beliefs in the topic of the guidelines. Studies around the world reported that the low level of knowledge and beliefs regarding the guidelines of antibiotics usage influence practices negatively [21], [78]. However, other studies reported dissonance between knowledge and practices as reported in this Indian study where doctors score high for knowledge and attitudes but poorly performed practices [79]. Probably, healthcare professionals' beliefs could influence adherence to clinical practice guidelines.

Overall, improving knowledge and aligning healthcare professionals' beliefs in guidelines is a key to good quality care and patient safety. We made data available in the Benin setting by assessing the knowledge and exploring healthcare professionals' beliefs in antibiotic prophylaxis.

Section 3

Ceasarean section and user fees exemption policy

Benin is a Sub-Saharan African country with average 12 million inhabitants. Its health system is organized as a pyramid in three levels: national referral teaching, and departmental and peripheral hospitals comprising State-owned and private facilities. The geographic accessibility to facilities is around 66%, and 44% of healthcare service utilization. This later low rate is due to the quality of care, the welcome and the limited financial resources of the population[80]. The healthcare fees are financed by patients by direct payment at the point of the service. It represents an average of 53% of household expenditures with a proportion of 76% dedicated to pharmaceutical products [80]. Contrary to the WHO recommendation, Benin does not reach Universal Health Coverage for all [81]. Only 9% of the population has health insurance coverage [82]. However, thanks to the intervention of the government with the support of international donors, there is fees exemption for immunization, contraception, care for Human Immunodeficiency Virus (HIV) and tuberculosis, cholera treatment during outbreaks, and mother and child healthcare [83].

User fees refer to a financing mechanism that has two major characteristics: the patient makes payment at the point of service use and there is no risk-sharing. User fees can comprise any combination such as medicines costs, medical consumables costs, and entrance or consultation fees. They are directly paid for each visit to a healthcare professional, although in some cases follow-up visits for the same episode of illness can be covered by the initial payment [84]. Since the 1980s, user fees have replaced tax-based

financing for government health services in Africa. The main objective given by national policy-makers for the introduction of user fees has been to raise revenue, on one hand, improve drug availability, and general quality of healthcare, and extend coverage on another hand [85].

Introduced in West African countries by the Bamako initiative in 1987, user fees were supported by four assumptions [83]:

- the strategy increases economic efficiency because limited resources are allocated to their most valuable use,
- it reinforces accountability of the public services and makes it more responsive to users fluctuating preferences and demands,
- it permits recovery of cost and increased equity,
- it is based on the concept of 'fairness' since the user pays only for the goods and services he or she uses.

It results in that user fees limits the access to care services and disease can be exacerbated with increases rate of death. "Medecins sans frontières" reported 8 ways user fees for health are harmful to people which are displayed in **Box.3** [86]:

Box.3 Eight ways user fees for health harm people according to "Medecins sans frantières"

1- People die or get sicker,
2- People receive sub-standard or incomplete treatments
3- Prevention of disease is reduced
4- treatment for disease requiring care over an extended period becomes more complex and, ultimately, more expensive
5- People become poorer
6- Patients are kept imprisoned in health facilities until they pay
7- Epidemics go unnoticed or underreported, delaying response
8- It's more difficult for vulnerable groups to access health services.

Médecins sans frontières, 2017

Others studies also reported that user fees collected at the point of use have been identified as a major barrier to seeking essential care, including skilled birth attendance at a health facility [84], [87]. To address this barrier, a user fees exemption policy was introduced in several low-income countries to improve access to health.

Indeed, low and middle-income countries implement the user fees exemption policy (UFEP) for financing expenditures on healthcare in order to protect poor populations from disease negative outcomes [88]. According to the WHO, health financing is a core function of health systems that can enable progress toward

universal health coverage by improving effective service coverage and financing protection [89]. It is the universal health coverage goal of the Sustainable Development Goals [81].

In sub-Saharan Africa, the user fees reduction and removal of public healthcare services have appeared as a fundamental instrument to move forward universal health coverage [90]. Studies reported that it affordes the access to curative and preventives services. Introduced for maternal and children's care especially in caesarean section in some African countries, UFEP improves the access to obstetric services, reduces the mortality of mothers and newborns, and decreases the stress on healthcare professionals in maternities and burden on families [91].

User fees exemption for mother and child healthcare has been introduced in Benin in 2009 as in many sub-Saharan African countries such as Burkina Faso, Mali, Ghana, Sierra Leone, and Senegal [83], [92]–[94]. The aim of introducing such policy is to improve the access to healthcare services, especially the caesarean section to reduce the rate of maternal and neonatal mortalities as recommended by Sustainable Development Goal No.3 [95]. In Benin, these rates are high (in 2014: maternal mortality was 347 for 100,000 deliveries and neonatal 37.8 for 1,000 childbirths), but their reduction is among the health issues priorities [96]. In addition to the aim of reduction of maternal and neonatal mortalities, the user fees exemption policy of the caesarean section in Benin has a particular agenda: to avoid the detention of the patient (mother and

newborn) because of the unpaid bill [83]. This policy costing FCFA 3 billion (US$ 4,840,.200) per year has increased the rate of caesarean section (from 3.6% in 2006 to 6.2% in 2010) [97] and decreased the financial burden on patients and families [91]. The policy was managed by a national agency "Agence National de la Gestion de la Gratuité de la Césarienne, ANGC" which among many prerogatives reimbursed FCFA 100.000 (US$166) per each caesarean section performed in approved hospitals. This amount included the surgical procedure fees and all the necessary materials and medicines needed including antibiotics. These materials and medicines are gathered in a national kit. A stock of this kit was freely provided to the approved hospital at the launch of the policy like an endowment. From the end of this stock, each hospital should make its kits locally based on the national kit list and perform freely cesarean sections for patients. According to data in the literature, this endowment resulted in a misunderstanding since most of the hospitals thought that the government will continuously provide the kits and in the same time reimburse the amount of FCFA100.000 (US$166) [98]. In Mali, hospitals receive FCFA30,000 (US$50) for a simple caesarean section and FCFA 42,000 (US$70) for a complicated caesarean section in addition to a surgical kit available [99]. Since January 2022, the ANGC has been dissolved by the Benin government, and its prerogatives were transferred to "Agence Nationale de la Protection Sanitaire, ANPS", but the fees exemption policy for caesarean section is still running in the hospitals [100].

After the first years of implementation of the use fees exemption policy, studies have identified bottlenecks in its success such as:

- at the national level: poor planning, insufficient allocation of resources, delays in distribution of resources, and insufficient communication [88], [101],
- at the operational level: the concept of 'street-level bureaucracy which has been used to explain persistent charging of fees[90], [102],
- at the individual level: the poor quality of care provided to patients with its consequences and the decrease of the engagement of healthcare in the care since they cannot perceive money from patients or their parents [84], [103], [104].

Although these bottlenecks influencing the implementation of the policy are important, little is known about how medical consumables and medicines are made available in the context of the policy to fulfill the agenda of care providing. In the frame of this thesis, we investigate the user fees exemption policy for caesarean section formulation in Benin, focusing on the selection of antibiotics in the national free kit. We presented our preliminary findings in the paper included in chapter 4.

AIM AND OBJECTIVES

Aim and objectives

As it is known, Infection Prevention and Control program contributes to reducing the harm due to HAIs and AMR, and one of the key components is the use of antibiotics. To take part in this action, the main aim of this thesis is to **"identify the bottlenecks for the rational use of antibiotics in caesarean section in Benin."** In order to reach our aim, we worked to identify and analyze the determinants that can influence the rational use of antibiotics in caesarean sections in Benin. We then responded to specific research questions outlined as follows:

1- What are the practices of the utilization of antibiotics before, during, and after caesarean section?
2- What are the level of knowledge and beliefs of healthcare professionals on antibiotic prophylaxis in Benin?
3- What is the influence of user fee exemption policy formulation on the practices of antibiotic prophylaxis in Benin?
4- What is the contribution of the patient to infection prevention and control in surgery in Benin?

To answer our research questions, we collected data on different aspects of the subject in four hospitals located in the South (one national referral, two zonal, and one confessional peripheral).

The four hospitals were chosen based on the pyramidal structure of Benin health system in intention to compare data

between hospitals and to appreciate if difference is between pratices. Firstly, we collected data on antibiotic use on three levels: before, during, and after caesarean section (prophylaxis and therapy). To better understand our previous data which showed a poor achievement of antibiotic prophylaxis, we assessed the knowledge and explored the beliefs of healthcare professionals on antibiotic prophylaxis since these parameters lead the practices [76], and the WHO reported low adherence to surgical teams to antibiotic prophylaxis guidelines [30].

During the interviews with healthcare professionals, we noted that they had low confidence in the quality of antibiotics in the kit, and expressed the absence of the antibiotics therein. To document their statements, we assessed the availability of injectable antibiotics in hospital pharmacies and performed their chemical quality analysis. This chemical analysis also helped to provide data on the quality of injectable antibiotics in Benin since there is a great spread of substandard and falsified drugs in low-income countries [61], and the national laboratory of quality control (Agence Nationale de Contrôle de Qualité des Produits de santé et de l'eau: ANCQ) often performs analysis on oral forms of medicines.

In the qualitative study, the healthcare professionals expressed some disagreement with the user fees exemption policy and the antibiotics selected in the kit. To understand this situation, we performed a qualitative study on policymakers involved in the formulation of the policy and the selection of antibiotics. From the

studies performed since the launch of this policy, some negative consequences of the implementation on other aspects of care (under-table payment to healthcare professionals, additional medical prescriptions including antibiotics, lack of information on the policy for patients, poor quality of the care provided in terms of the long delay of caesarean section initiation, the occurrence of post-operative infections,…) were reported [83], [98], [103], but there is no data on the utilization of the antibiotic available in the kit.

In five chapters, we displayed the findings of our different studies. In the first one, we documented the antibiotics utilization in a population of women having a caesarean section. In the followings, we identified and analyzed the determinants: Healthcare professionals' determinants (chapter 2), Injectable antibiotics' availability and chemical quality's determinants (chapter 3), Policy makers' determinants (Chapter 4), and Patients' determinants (Chapter 5). **Figure 3.** displays the organization of the five chapters.

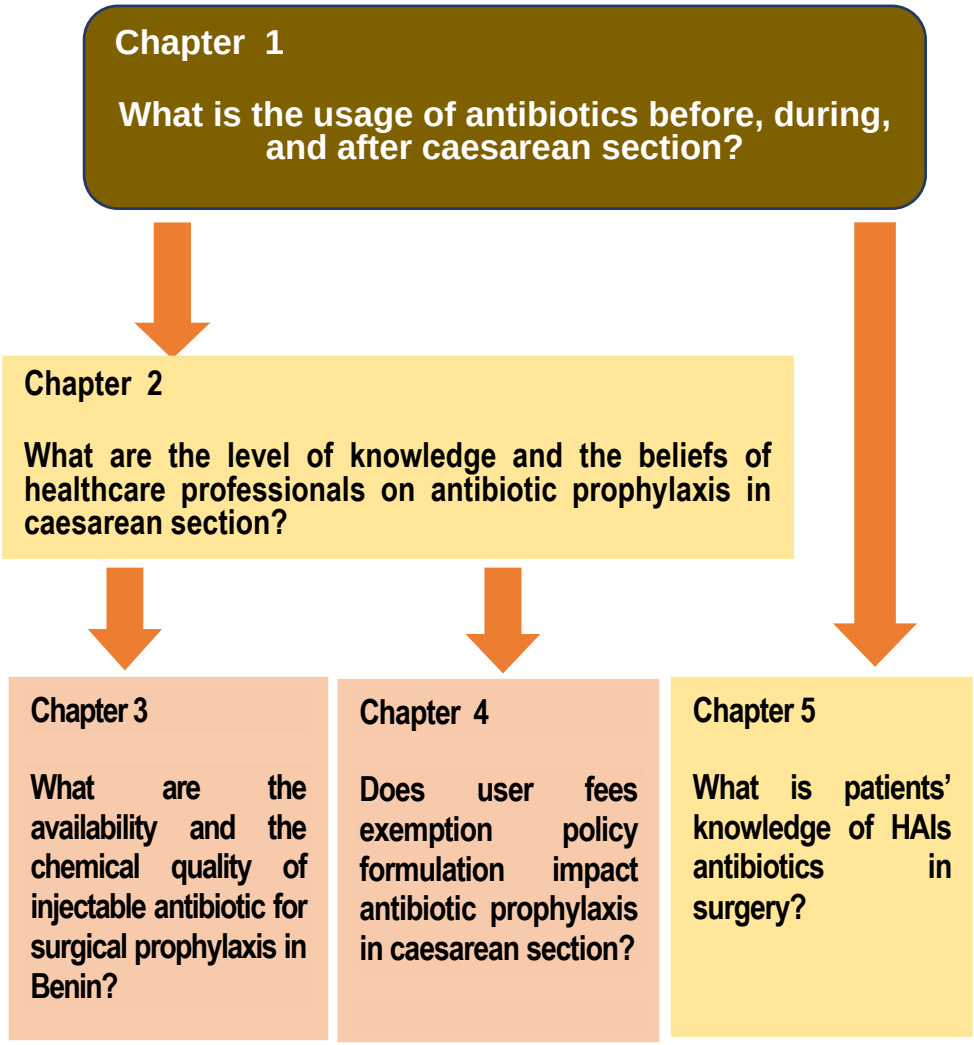

Figure 3. Our thesis' overview

Results

Results

CHAPTER 1: Antibiotic usage in patients having undergone caesarean section: a three-level study in Benin.

Chapter 1 overview

In this study, we collected data on antibiotics usage before, during (antibiotics prophylaxis), and after caesarean section in four hospitals.

Background

- Self-medication with antibiotics is spread in low- and middle-income countries.
- Antibiotic prophylaxis practices are inappropriate worldwide with a high rate of poor postoperative outcomes.
- The misuse and overuse of antibiotics are undoubtedly the main factors associated with the high numbers of antibiotic-resistant pathogenic and commensal bacteria worldwide.

Inputs from this chapter

From our investigation of 141 patients:

- A proportion of 56.7% of patients having caesarean section had used antibiotics before admission. The majority of them had erroneous knowledge of the indication of antibiotics.
- Only 31.2% of antibiotic prophylaxis practices was conform to the kit. Globally, three of the five conventional criteria were less achieved (inappropriate choice of antibiotic, under dosage, and long duration of administration).

- The broad-spectrum antibiotics were used after caesarean section in the absence of documented infection.

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Article

Antibiotic Usage in Patients Having Undergone Caesarean Section: A Three-Level Study in Benin

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Abstract: The intense use and misuse of antibiotics is undoubtedly the main factor associated with the high numbers of antibiotic-resistant pathogenic and commensal bacteria worldwide. In low-income countries, this misuse and overuse is widespread, with great consequences at the personal and global levels. In the context of user fee exemptions in caesarean sections, we performed a descriptive study in women to assess the use of antibiotics on three levels—antenatal, during caesarean section, and postpartum—in four Beninese hospitals. Out of the 141 women included, 56.7% were using antibiotics. More than the half (71.3%) were taking more than one antibiotic, either for a long time or in acute treatment. In prophylaxis, the timing, dose, and duration of administration were not correctly achieved. Only 31.2% of women received optimal antibiotic prophylaxis. Various antibiotics including broad-spectrum molecules were used in the patients after caesarean section. The use of antibiotics was improper on the three levels studied. The high rate of self-administered antibiotics, the poor achievement of antibiotic prophylaxis, and the postpartum overuse of antibiotics showed a poor quality of care provided in pregnancy. A national policy is essential to improve the use of antibiotics by the general public as well as by professionals.

Keywords: caesarean section; antenatal antibiotic use; antibiotic prophylaxis; postpartum antibiotic use; Benin

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1. Introduction

The intense use and misuse of antibiotics is undoubtedly the main factor associated with the high numbers of antibiotic-resistant pathogenic and commensal bacteria worldwide [1]. The resistance of bacteria to antimicrobials has become one of the most serious global public health threats in this century, with the greatest impact in developing countries, where the burden of infectious diseases is much higher [2,3]. The World Health Organization (WHO) says that steps can be taken at all levels of society to reduce the impact and limit the spread of resistance [4], by reducing the incidence of infectious diseases, increasing knowledge and awareness, and promoting rational use of antimicrobials, among other measures [5]. This kind of action can be effective when data on antibiotic use and antimicrobial resistance evolution are available.

Antibiotics in pregnancy are used to treat the infections encountered during this physiological state, such as urinary tract infections, pyelonephritis, sexually transmitted

infections, and upper respiratory tract infections [6]. A limited number of antibiotics are considered safe and effective in pregnancy, and their use has to be based on a risk-versus-benefit decision [7]. In low-income countries such as Benin, the antibiotics used come from medical prescriptions or direct purchase from a pharmacy. Studies have shown that the poor quality of the prescription of antibiotics in patients [8], along with the possibility of purchasing antibiotics without medical prescription, has significant consequences in terms of antimicrobial resistance [9]. Antibiotics are also used when women have to undergo caesarean section for prophylaxis. Antibiotic prophylaxis is defined as "a brief course of an antimicrobial agent initiated before an operation begins in order to reduce intraoperative microbial contamination to a level that will not overwhelm host defence and result in infection" [10]. Conventionally, antibiotic prophylaxis must meet five criteria: indication, choice of molecule, dose, timing, and duration [11]. The objectives of antibiotic prophylaxis are, firstly, to achieve sufficient antibiotic tissue concentration before possible bacterial wound contamination and, secondly, to ensure adequate levels throughout the operative procedure to prevent subsequent bacterial growth [12]. Antibiotic prophylaxis is shown to lower the incidence of infection after surgeries [13]. Although antibiotic prophylaxis recommendations are known worldwide, studies have shown that surgical teams have low adherence to respecting those recommendations [14]. Adherence to recommendations in Benin is unknown.

Caesarean section has been known to increase the rates of maternal infectious morbidities fivefold compared to vaginal delivery. Antibiotic prophylaxis can play a major role in improving caesarean-section-associated risks of infections, such as endometritis, surgical site infections, and urinary tract infections [15,16]. The practice of antibiotic prophylaxis according to the guidelines decreases the poor outcome consequences of caesarean section, such as long hospital stays, systematic antibiotherapy leading to overuse or inappropriate use of antibiotics and the development of antimicrobial resistance, additional costs, and psychological and social impacts [16].

In 2009, the Government of Benin set up a policy of user fee exemptions for caesarean sections, and an agency was created to manage the policy. A free kit containing the required medicines—including antibiotics (injectable: 1 g ampicillin, 500 mg/100 mL metronidazole, and 80 mg/2 mL gentamicin for prophylaxis; and in oral forms: 500 mg amoxicillin and 500 mg metronidazole tablets for postpartum)—and materials needed for the procedure is available.

Unlike in high-income countries, data on the use of antibiotics are scarce in low-income countries, where hygiene conditions are poor and antimicrobial resistance is of great concern [17]. In Benin, several studies have reported an increasing evolution of antimicrobial resistance [18–20], but there are no updated data on antibiotic use. Moreover, the use of antibiotics in caesarean section has not been described since the implementation of the caesarean section user fee exemption in Benin. To make data available in Benin, we aimed to document the use of antibiotics in a population of women undergoing caesarean section in four hospitals in Benin, by conducting a descriptive study on three levels: antenatal (a patient's medication history in terms of antibiotics used prior to hospital admission), an audit of surgical antibiotic prophylaxis for caesarean section, and the postpartum use of antibiotics.

2. Results

In total, 141 women were included in our study. The patients' age range was 17–42 years, with a median of 28 years; 81.60% of the cases (n = 115) were emergency, and 27.60% (n = 39) were referred from another hospital. The median duration of the intervention was 39.20 min, ranging between 13 and 75 min. Among the patients, 8.5% (n = 12) had a chronic disease (e.g., diabetes, sickle cell anemia, cardiovascular or hepatic disease). Patients' demographic and clinical characteristics are displayed in Table 1.

Table 1. Patients' demographic and clinical characteristics.

Hospital Studied	Parameters	Hosp1	Hosp2	Hosp3	Hosp4	Total
Demographic characteristics	Number of patients, *n* (%)	50 (35.50%)	49 (34.70%)	22 (15.60%)	20 (14.20%)	141 (100%)
	Median age (years) ± standard deviation	28.6 ± 5	27.4 ± 5.9	27.9 ± 4.4	28.1 ± 3.8	28 ± 4.8
	Range	(20–42)	(17–41)	(21–37)	(22–37)	(17–42)
Clinical characteristics	Emergency cases, *n* (%)	35 (70.0%)	44 (89.80%)	21 (95.50%)	15 (75.0%)	115 (81.60%)
	Referred cases, *n* (%)	16 (32.0%)	16 (32.60%)	6 (27.30%)	1 (5.0%)	39 (27.60%)
	Median intervention duration (minutes) ± standard deviation	48.0 ± 14.8	37.40 ± 10.1	35.70 ± 10.1	35.30 ± 13.0	39.20 ± 12
	Range	(24–85)	(13–75)	(22–53)	(19–69)	(13–75)

3. Antenatal Antibiotic Use

We interviewed 141 patients about their medication with antibiotics prior to their admission to hospital; 80 (56.70%) of them declared they were using antibiotics. A total of 23 (28.70%) were taking one antibiotic, and more than half (57 of 80; 71.30%) were taking 2–5 antibiotics, either for a long time (more than 15 days) or in acute treatment. The most frequent antibiotic used was amoxicillin in monotherapy (n = 16, 20.0%), or combined with metronidazole (n = 14, 17.50%) or ciprofloxacin (n = 12, 15.0%). Other antibiotics (e.g., ampicillin, cloxacillin, erythromycin, co-trimoxazole) were used by 38 of them (47.50%).

Nearly half of the patients (n = 38, 47.50%) were taking antibiotics under their own initiative. Almost the same proportion (n = 36, 45.0%) indicated that the antibiotics were prescribed by a healthcare professional, but more than half could not give the precise reason for the prescription. The remaining women (n = 6, 7.50%) were using antibiotics based on the recommendations of their relatives. In the case of their own initiative, patients declared having the information from a previous medical prescription. This could be due to the fact that the prescribers did not educate patients after prescription to avoid inappropriate use of antibiotics.

Among the indications (e.g., malaria, fever, pain, infectious diseases), stomach trouble was the most frequent indication declared by the patients (n = 13, 16.30%). The patients did not bring their medicines to the hospital.

The overview of the use of antibiotics prior to hospital admission is reported in Table 2.

Table 2. Repartition of the utilization of antibiotics prior to admission.

Patients (N = 141, 100%)	Characteristics *n* (%)
Patients who used antibiotics	80 (56.70%)
Number of antibiotics used	
1	23 (28.70%)
2 to 5	57 (71.30%)
Antibiotics used	
Amoxicillin	16 (20.0%)
Amoxicillin + metronidazole	14 (17.50%)
Amoxicillin + ciprofloxacin	12 (15.0%)
Others (ampicillin, cloxacillin, erythromycin, co-trimoxazole)	38 (47.50%)
Type of use	
Self-administration	38 (47.50%)
Medical prescription	36 (45.0%)
Relatives' advice	6 (7.50%)

4. Antibiotic Prophylaxis in Caesarean Section

The antibiotic prophylaxis practices were assessed by the five conventional criteria (indication, choice of molecule, dose administered, timing, and duration of administration) in the four hospitals. Four of the five criteria were less appropriately achieved. Only 31.2% (44/141) of women received optimal antibiotic prophylaxis, i.e., correct antibiotic

prophylaxis according to the five criteria. Sixteen different antibiotic regimens were observed; three of them contained the three molecules of antibiotics from the kit, and were administered in 17.0% of patients (24/141). The most frequent regimen administered was amoxicillin + clavulanic acid combined with metronidazole in 27.0% (38/141), which represented 70.4% (38/54) of patients who received the antibiotics not included in the kit.

From the data collected in the four hospitals, the levels of achievement are represented in Figure 1.

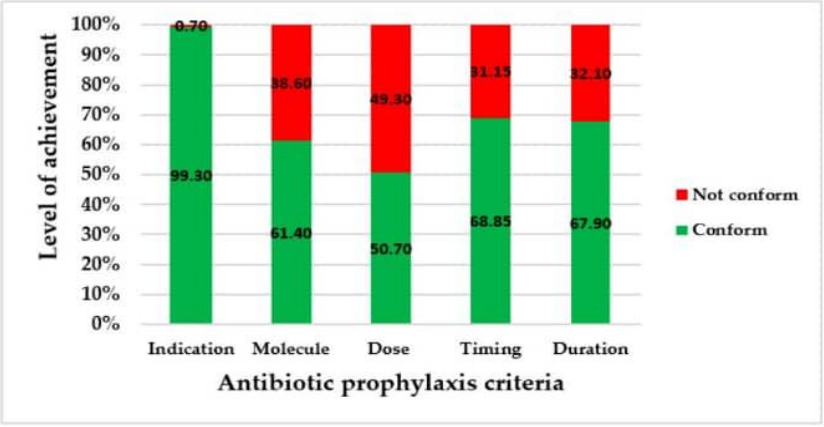

Figure 1. Levels of achievement of conventional criteria for antibiotic prophylaxis.

5. Postpartum Antibiotic Use

After caesarean section, all 141 patients received oral antibiotics for 5 to 10 days, depending on the prescriber. The oral antibiotics (amoxicillin + metronidazole) included in the kit were used by 48.2% (68/141) of the women. The others 57.7% (73/141), in addition to metronidazole, received out-of-kit and broad-spectrum antibiotics, such as amoxicillin + clavulanic acid in 43.3% (61/141), lincomycin in 7.8% (11/141), and cefixime in 0.7% (1/141). The broad-spectrum antibiotics used were variable from one hospital to another. Each hospital used the same broad-spectrum antibiotic in all of their patients. We did not record any diagnosis for the use of postpartum antibiotic therapy.

6. Discussion

Our study describes the perinatal use of antibiotics in women who underwent caesarean section in four different hospitals in Benin.

Firstly, the medication history showed the use of antibiotics prior to hospital admission in 56.7% of the women. This rate was higher than that reported in the Democratic Republic of Congo in 2013 (12.3% of patients admitted in emergency) [21], and represents an enormous concern in developing countries. Merrett et al. stated that self-medication with antibiotics in low- and middle-income countries is widespread, and leads to overuse and misuse of antibiotics, with consequences on the personal and global levels [22]. Some of the patients in our study were taking antibiotics based on medical prescription; others did so as self-medication, and declared that this habit was based on a former healthcare

professional's prescription, or on relatives' advice. The large proportion of self-medication noted could be due to the fact that patients could buy antibiotics without medical prescription at the time we collected the data. Although we did not collect data on the women's knowledge and education levels, we know from the literature that the low levels of those parameters negatively impact behaviors regarding medication [23], and that women in Benin are less educated than men [24]. Socioeconomic and behavioral factors (e.g., out-of-pocket payments, absence of health insurance, level of education, and culture) were reported to explain the self-medication [3,25,26]. From the analysis of our data, we can hypothesize a lack of useful required information provided by healthcare professionals in outpatient care. Indeed, the patients could not explain their precise reasons for taking antibiotics. Additionally, some of the pregnant women had used ciprofloxacin, while the use of fluoroquinolones should be avoided unless the benefits outweigh the risks [7]. This shows the poor quality of healthcare delivered in our country, as reported in the second edition of "Disease Control Priorities in Developing Countries", with a need for improvement [27]. One of the most important ways to improve health in developing countries is by educating citizens. Educating people enables them to increase their health literacy, take preventive healthcare measures, avoid riskier health behaviors, and demand better quality healthcare services [27]. Considering the enormous threat that antimicrobial resistance represents to public health, and the place of mothers in families' health (in most households, women are the managers of their families' healthcare needs) [28], educating pregnant women will help not only them and their babies, but also other members of their families, to avoid inappropriate use of antibiotics.

Secondly, our study identified improper practices of antibiotic prophylaxis in caesarean section. Apart from the indication that was conformed to by 99% of the patients, either in the operating room or in the recovery room, the four other criteria (molecule, dose, timing, and duration) were not appropriately applied in at least 30% of cases. A proportion of 49.30% of patients did not receive the correct dose of antibiotic. The criterion of the dose administered was the least appropriately achieved.

Under one-third of women (31.20%, 44/141) received antibiotic prophylaxis with the five conventional criteria correctly properly achieved. The aim is that antibiotic prophylaxis should be correctly achieved in 100% of cases. However, this compliance rate was higher than those reported in a Jordanian study (2.70%) [29] and in a Greek study (0%) [30]. This finding can be explained by the availability and use of the antibiotics in the kits in some of the hospitals studied. This proportion has to be improved on, especially since it has been reported that the use of the kits significantly enhances the national guidelines on the surgical application of antibiotic prophylaxis [31].

Although all of the patients received a prophylaxis, non-conformities were observed, such as for the timing in 31.10%, versus 0% in a Greek study [30] and 11.60% in a Sudanese study [16]; the dose administered, with 49.30% of women under-dosed versus 37.50% in a Jordanian study [29]; and the duration of administration, exceeded in 32.10% of patients, in contrast to 88.20% reported in a Jordanian study and 97% in a Sudanese study [10,29]. The consequences of these non-conformities are numerous. The delay in timing reduces the patient's protection during surgery, and can lead to the occurrence of postoperative infections. The optimization of the initial dose of antibiotics in prophylaxis is important in order to establish an inhibitory concentration of the drug in the serum and tissues by the time the skin is incised [11]. Concerning the under-dosing, it results in low plasma concentrations of antibiotics, leading to a risk of surgical site infections or endometritis [11]. The long course of intravenous administration contributed to an overuse of antibiotics for prophylaxis. A continued course of antibiotic prophylaxis pressurizes the nurses, and affects their workload [12]. The delay of timing and long duration of prophylaxis induce financial burden for patients, because postoperative expenses due to infections are not taken into account in the Benin user fee exemption policy, and patients must pay for the additional needed and prescribed antibiotics outside the kit in order to complete the antibiotic prophylaxis duration. The WHO recommends a single dose of antibiotic [11], as

concluded in a randomized study performed in other low-income countries [12,32]. This finding appeared paradoxical in this study, meaning that antibiotic prophylaxis was not administered with good timing and dose, but beyond the recommended duration. This attitude could be due to the fear of post-caesarean infections caused by the particular problems that low-income countries such as Benin experience, as the women accumulate all factors causing the high rate of maternal mortality, such as suboptimal health status, nutritional deficiencies, lack of hygiene, scarce resources, and inadequate knowledge [12]. This fear thus induces the use of broad-spectrum antibiotics. In fact, despite the availability of antibiotics in the kit, amoxicillin + clavulanic acid was used in 26.9% of cases, ceftriaxone in 3.5%, and ceftriaxone + sulbactam in 0.7%. This finding is consistent with those reported in a Sudanese hospital, where broad-spectrum antibiotics were used in 56.3% of cases in spite of the availability of the recommended antibiotic (cefazolin) [10]. This point highlights a veritable problem of adherence to the guidelines by the surgical teams, and results in the irrational use of antibiotics and increases the occurrence of antimicrobial resistance [10].

In addition to the cost the prescription of out-of-kit antibiotics represents (three boxes of amoxicillin + clavulanic acid cost USD 10.57–16.95, versus free antibiotics in the kit), patients have to face the non-availability of these prescribed antibiotics in the hospital pharmacies. Thus, patients were often obliged to buy antibiotics from private pharmacies. In view of the fact that most of the women were presented in an emergency situation (81.6% of cases) and/or often were referred from peripheral health centers, the availability of the required antibiotics in the hospital pharmacy becomes essential. This will be a national challenge for Benin in the coming years, as has been reported in other low-income countries, such as Mozambique [12].

Finally, in the postpartum use, antibiotics were available in Benin's free kit by providing oral antibiotics (amoxicillin + metronidazole). According to the WHO, the antibiotics recommended are the combination of clindamycin and gentamycin as first-line treatment for postpartum endometritis [33]. In the case of the women included in our study, no diagnosis of endometritis or other infection was made, but broad-spectrum antibiotics (e.g., amoxicillin + clavulanic acid, lincomycin, cefixime) were used in several cases. However, although the antibiotics provided in the kit are intended for postpartum endometritis, it is important to note that they are different from the one recommended by the WHO (clindamycin), which is not currently available in Benin.

The global analysis of the use of antibiotics in the patients who underwent caesarean section in the four hospitals chosen, following the three levels of the healthcare system in Benin, highlighted either inappropriate use, misuse, or overuse of antibiotics. Although practices were similar, showing a local consensus within each hospital, the healthcare professionals in high-level hospitals were less adherent to the kit. In sum, we found a poor quality of care provided for pregnancy, since quality of care in obstetrics is a continuum that spans the pre-pregnancy, pregnancy, and postpartum periods. Regarding the context of the increased spread of bacterial resistance, rational use of antibiotics would benefit public health, as well as the patients' and the hospitals' finances.

To improve the use of antibiotics in Benin, various levels of the healthcare system have to be taken into account. First of all, patients could be educated in hospitals or through mass media by providing information on antibiotics (e.g., when to use, resistance problems, and prevention measures to avoid infections). Secondly, it is important to raise the level of knowledge of the healthcare professionals in terms of the prescription of antibiotics, to conduct audits and feedback in hospitals, and to provide local and consensual guidelines for the use of antibiotics. Setting up a multidisciplinary team in hospitals can also help to improve the use of antibiotics. Thirdly, at the central level, a national policy is essential to coordinate activities by providing data on antibiotics consumption and antimicrobial resistance, along with directives and strategies to improve utilization.

To the best of our knowledge, our study is the first to analyze the use of antibiotics before, during, and after caesarean section in Benin and in various types of hospitals. Observations were conducted 24 h a day, 7 days a week. However, this study has some

limitations: All of the observed hospitals were from the southern part of the country; thus, they are not entirely representative. The sample size was relatively small. In addition, there was no assessment of factors associated with inappropriate use of antibiotics. Nevertheless, we are confident that our findings will help to raise knowledge about the use of antibiotics in Benin, and help to perform this kind of study in other areas of the country.

7. Materials and Methods

In obstetrical wards of 4 hospitals located in the south of Benin, we performed a three-level study on antibiotic use in patients who were undergoing caesarean section. Patients were approached in the operating theatre when medical staff were preparing the intervention. The study was briefly explained in the patient's language. The sampling followed the inclusion and exclusion criteria as described in the document entitled "L'audit clinique: bases méthodologiques de l'évaluation des pratiques professionnelles" [34], with the objective of having at least 100 cases of caesarean section observed during the study period for this first insight into antibiotic use in Benin.

We recorded patients' medication history by interviewing the patients on their habits of using antibiotics prior to admission, conducting a prospective observation of the antibiotic prophylaxis practices, and determining postpartum antibiotic use from medical charts. The four hospitals have different characteristics, but they are all approved to practice free caesarean section. They included one teaching referral hospital (hosp1: 254 beds), two teaching zonal hospitals (hosp2: 101 beds and hosp3: 116 beds), and one confessional hospital (hosp4: 81 beds). Each hospital included in this study provided written authorization to perform all of the steps of the study. Over a period of 1 month (November to December 2016), observers' teams collected data from patients undergoing caesarean section with class 2 surgical wound contamination (clean–contaminated wound, any infection diagnosed before caesarean section), using two survey forms (Appendices A.1 and A.2)."

Form No. 1 was used to collect data on demographic characteristics (e.g., name, age) and patients' medication history (e.g., oral antibiotics used, indication for utilization, author of the prescription, regimen of administration). The patients' medication history was recorded after the intervention in the hospitalization rooms.

Form No. 2 is divided into two parts: The first part helped to collect data on demographics (e.g., name, age)—in order to be sure that we were collecting data from the same patient as the previous form—intervention date in the operating theatre, dates of admission and intervention, type of procedure (urgent or elective), and antibiotics used for prophylaxis (molecule, dose, timing, and duration). This part of the form was adapted from those used by the WHO and the Scientific Institute of Public Health, Belgium [35,36].

In the second part of form No. 2, we collected follow-up data during hospitalization from medical charts, including intravenous antibiotics used after caesarean section (name, dose, posology, and duration), and the postpartum use of oral antibiotics i.e., after delivery (name, dose, posology, and duration).

Observers' teams consisted of four pairs of students of the health science faculty. After a training session with the main researcher, the four pairs tested the applicability of the forms in two other hospitals that were not included in the present study. After the test, a debriefing took place, and some questions were reviewed. During data collection, one observer included patients after obtaining their consent, and recorded data in the operating theatre during the caesarean section procedure using the first part of form No. 2. The second observer recorded data in the hospitalization rooms until the end of the intravenous administration in the second part of form No. 2. Patients were included alternatively in different periods of the day (intervention in the morning, afternoon, evening, and night) in order to see whether practices changed from time to time.

The practices of antibiotic prophylaxis were assessed based on the following five conventional criteria [11]:

Indication: In caesarean section, antibiotic prophylaxis was always considered to be indicated.

Choice of antibiotic: The conventional recommended antibiotic is cefazolin. In Benin, cefazolin is not available. The Benin caesarean kit instead contains ampicillin, metronidazole, and/or gentamicin. The choice of antibiotic was considered to be correct if the antibiotics from the kit were used.

Timing of administration: Guidelines recommend administration of the first preoperative dose 30–60 min before incision.

Accuracy of the first preoperative dose(s): Double the usual adult dose of an antibiotic is recommended for caesarean section. Any necessary subsequent doses are administered at the usual adult dose.

Duration of prophylaxis: In caesarean section, antibiotic prophylaxis can be administered in a single dose, or for a period of 24 h maximum.

Data were analyzed using IBM Corp (released 2016; IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp). Descriptive statistics presented continuous variables using medians (with 25–75th percentiles), because they were not normally distributed, and categorical variables are presented as numbers and percentages.

8. Conclusions

Caesarean section is a life-saving intervention. The conventional recommended antibiotic use is for prophylaxis, which is an incontestable parameter to ensure quality of life for patients. Despite the availability of a free kit containing the antibiotics required, antibiotic prophylaxis was poorly achieved in Benin. In the use of antibiotics prior to hospital admission, patients were insufficiently informed for the precise reason of their use if they had a medical prescription. In the postpartum period, there was no diagnosis of postoperative infection that could require the use of antibiotics. In sum, self-administered antibiotics require particular attention in order to reduce their rate and long-term consequences. Various measures should be embedded in a national policy to ameliorate the use of antibiotics by the general public and by professionals in Benin.

Author Contributions: A.M.D. wrote the protocol, conducted the study, conducted data analysis, and wrote the paper; V.O.B. assisted with the data analysis and commented on the paper; L.A.Y. commented on the paper; S.A. commented on the paper; F.V.B. commented on the protocol and the paper; T.V.H. commented on the paper; F.M.D. commented on the paper; O.D. commented on the protocol, assisted with the data analysis, and commented on the paper. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by each of the four hospitals' ethics committees by providing written authorization to perform the study. Authorization documents will be available upon request.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

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Conflicts of Interest: Not applicable.

Appendix A

Appendix A.1. Antibiotics Use in Patients Underwent Caesarean Section: Medication History

Date of collect: … / … / … …

Patient identity: … … … … … … … … … … … … Patient age: … … … … … … …

Hospital: … … … … … … … … … …

Do you use to take antibiotics? Yes ☐ No ☐

Which antibiotic do you use to take? Ampicillin ☐ Amoxicillin ☐ Ciprofloxacin ☐ Cotrimoxazole ☐ Erythromycin ☐ Metronidazole ☐ Doxycycline ☐ Other (write the name): ……
Who prescribed this antibiotic for you? ……
How long have you been taking it? …… (days, months, years)
How often do you take it? Usually ☐ Often ☐ Rarely ☐ If needed ☐ **For which disease?** :……
Are you taking this antibiotic during your hospitalization? Yes ☐ No ☐

Appendix A.2. Use of Antibiotics in Prophylaxis and Post-Partum in Caesarean Section

Date of collection … … … … … … … … sheet N … … …

Hospital: … … … … … … …

Nota Bene

(a) Use one form per patient
(b) Pay attention on inclusion criteria.

I Patient data

Name and first names: …

(Will not be published)

Birthday or age of patient: …

Chronic disease/Comorbidity

☐ Diabetes (type … .) ☐ Cardiovascular disease: … … … … … … …

☐ Liver disease: … … … … … … … … … ☐ other: … … … … … … … … … … …

Transferred from other hospital: ☐ Yes ☐ No

Timing of intervention after transfer: … … days … … hours

II Surgical intervention

Date of intervention: … … / … … / … … …

Type of wound contamination: … … … … … … … … … (Class 2)

Duration of intervention: … … … … hours … … … minutes

Type of intervention ☐ Elective ☐ Emergency

Part 1

III Antibiotic prophylaxis

Is antibiotic prophylaxis realized Yes ☐ No ☐

Oral route ☐ Intra-venous ☐

Timing of administration before incision ☐ after incision ☐

Time of antibiotic's administration

If before incision: — days — hours — minutes
If after incision: — days —hours — minutes

Names of antibiotics administered

(1) …
(2) …
(3) …

Dose of antibiotics administered:

(1) …
(2) …
(3) …

(Re) Administration of antibiotics during intervention

☐ No ☐ Yes Time: … … … hours … … … minutes.

Administration of antibiotics in wake up room

☐ Yes ☐ No

If yes, name of antibiotics, dose, route of administration and duration:

(1) …
(2) …
(3) …

Part 2

Administration of IV antibiotics in hospitalization room: (Name, dose, and duration)

(1) …
(2) …
(3) …

IV Oral antibiotic in post-partum (Name, dose, and duration)

(1) …
(2) …
(3) …

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CHAPTER 2: Healthcare professionals' knowledge and beliefs in antibiotic prophylaxis.

Chapter 2 overview

The study in this chapter is conducted in a convergent parallel design. As described by Creswell et al. in 2011 [105], we concurrently conducted the quantitative and qualitative data collections in the three hospitals from the 4 included in the previous study. In a quantitative study, we collected data on the knowledge of antibiotic prophylaxis, and in a qualitative study, we explored the healthcare professionals' beliefs in antibiotic prophylaxis. We analyzed the two components independently and interpreted the results together.

Background

- Healthcare professionals' knowledge is often based on their vocational education.
- Studies reported a low level of knowledge of antibiotic prophylaxis in low-income countries with rare planning of trainings in hospitals.
- Healthcare professionals believe more in their experience than in guidelines.

Inputs from this chapter

- The mean level of knowledge of antibiotic prophylaxis criteria was 3.3 out of 5. Only 15.2% of healthcare professionals gave the 5 good responses to the 5 conventional criteria of antibiotic prophylaxis.

- Healthcare professionals lacked confidence in the antibiotics in the kit and expressed some disagreement about the policy formulation and the choice of the antibiotics in the kit.
- Several determinants such as “Patient health determinants”, “healthcare professionals’ determinants”, “hospital-related determinants”, “Central and structural organization determinants” and “Patient behavior determinants” lead to poor quality of antibiotic prophylaxis in terms of overuse and misuse of antibiotics.

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Article

Healthcare Professionals' Knowledge and Beliefs on Antibiotic Prophylaxis in Cesarean Section: A Mixed-Methods Study in Benin

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Abstract: A low adherence to recommendations on antibiotic prophylaxis has been reported worldwide. Since 2009, cesarean sections have been performed under user fee exemption in Benin with a free kit containing the required supplies and antibiotics for prophylaxis. Despite the kit, the level of antibiotic prophylaxis achievement remains low. We conducted a convergent parallel design study in 2017 using a self-administered questionnaire and interviews to assess the knowledge and explore the beliefs of healthcare professionals regarding antibiotic prophylaxis in three hospitals. Of the 35 participants, 33 filled out the questionnaire. Based on the five conventional criteria of antibiotic prophylaxis, the mean level of knowledge was 3.3 out of 5, and only 15.2% scored 5 out of 5. From the verbatim of 19 interviewees, determinants such as suboptimal patient status health, low confidence in antibiotics, some disagreement with the policy, inappropriate infrastructures and limited financial resources in hospitals, poor management of the policy in the central level, and patient refusal to buy antibiotics can explain poor practices. Because of the dysfunction at these levels, the patient becomes the major determinant of adequate antibiotic prophylaxis. Policymakers have to consider these determinants for improving antibiotic prophylaxis in a way that ensures patient safety and reduces the incidence of antimicrobial resistance.

Keywords: cesarean section; antibiotic prophylaxis practices; healthcare professionals; knowledge; beliefs; Benin

1. Introduction

In 2021, new research from the World Health Organization reported that the cesarean section (CS) rate was more than one in five (21%) of all childbirths globally . In developing countries, a rate of 8% of women gave birth by CS, with 5% in sub-Saharan Africa [1] A cesarean section can be a life-saving procedure, and prevents poor obstetric outcomes [2]. CS decreases the rate of maternal and neonatal morbidity, with a positive impact on women, especially in developing countries, where the CS rate is in the range of 5–10% [3]. However, a number of CSs have been reported to be non-medically justified, and could be harmful to the mother and her baby [4].

In the absence of universal health insurance coverage, the fear of medical, social, and financial implications of childbirth by CS decreases its affordability in developing countries [5]. To reach the Millennium Development Goal N.3, which consists of achieving universal health coverage [6], several African countries have implemented a user fee exemption policy [7]. User fees contribute to the unaffordable cost burdens imposed on poor households, and represent one facet of the social exclusion experienced by these households [8]. In recent years, several countries in sub-Saharan Africa have introduced user fee exemption policies to facilitate access to various maternal health services, including cesarean section [8]. In April 2009, the Benin government set up a national agency and approved 48 care facilities for their CS user fees exemption policy [9]. This policy improved the affordability of CS and resulted in an increase in its rate from 3.7% to 6.4% three years later [10], and a rate of 5.1% in 2018, reported by UNICEF [11]. The WHO reported a decrease in maternal mortality from 471 in 2009 to 397 per 100,000 deliveries in 2017 [12]. Although studies have reported a link between CS and maternal mortality [3], the report "Femhealth" of Centre de Recherche en Reproduction Humaine et en Démographie-Benin in 2014 concluded with a mixed appreciation [10]. The agency funds, by retroactive reimbursement, a fixed sum of 100.000 FCFA "Francs de la Communauté Financière Africaine" (an average of US$167 or 153.40 euros) for each CS performed in the approved hospitals [13]. This sum covers the check-up costs before the medical intervention, a kit (containing the materials and drugs required, including injectable antibiotics: ampicillin, gentamicin, and metronidazole; and oral antibiotics: amoxicillin and metronidazole), surgery, blood transfusion if needed and hospitalization for seven days [9] . Several studies have evaluated different components of the user fee exemption policy and their impact on its implementation and patients' opinions on CSs in Benin hospitals [14], [15]. After our observational study performed in 2016 in four hospitals in Benin, based on the antibiotics in the kit, our data showed improper practices of antibiotic prophylaxis [16] regarding the five conventional criteria, namely, indication, choice of the molecule, the timing of administration, the dose administered, and the duration of administration[17]. Infections during pregnancy are common, and other conditions, such as malnutrition, obesity, anemia, bacterial vaginosis, diabetes, group B streptococcus infections, and CS, may increase the risk [18]. However, when a CS is medically justified, antibiotic prophylaxis is essential to prevent poor post-operative outcomes [19]. However, the use of antibiotics in pregnancy, including the CS section, has to be weighted regarding the risk for women and babies (lactation), and the existing threat of antimicrobial resistance [20], [21]. In low-income countries such as Benin, because of the suboptimal health status and the lack of hygiene of the patients [22] , and the unclean state of the hospitals and infrastructures [23], women are more at risk for infections. Post-CS infections induce a high rate of expenses for patients, since these infections' treatment is not considered in the user fees exemption policies. From the data published in a study performed in Mali, 62.5–100% of women were infected post-partum, and expenses for antibiotics were higher than those of other post-partum complications [24] . Considering the burden infections represent for patients in low-income countries, prevention should be well-achieved. This study aimed to understand the determinants of the poor achievement of antibiotic prophylaxis by assessing and exploring healthcare professionals' (HcPs) knowledge and beliefs on antibiotic prophylaxis. By providing relevant data on those determinants, our study will help policymakers to set up interventions for improving antibiotic prophylaxis in Benin, and other countries with the same challenges.

2. Results

2.1. Assessment of the Level of Knowledge of Antibiotic Prophylaxis

A total of 35 healthcare professionals agreed to take part in the survey. The assessment of the HcPs' knowledge was based on data from 33 participants who completed the self-administered questionnaire. The response rate was 94.3% (33/35). Males represented

51.5% (17/33) of all participants; 60.6% (20/33) were nurse anesthetists; and the others (39.4%; 13/33) were physicians (anesthetists, anesthetists in specialization, and obstetricians). The median age and professional seniority were, respectively, 39.6 years old (range 23–57 years old) and 7.8 years (range = 1–22 years). The respondents' demographic characteristics are displayed in Table 1.

Table 1. Demographic characteristics of HcPs included in the survey.

Number of HcPs, N	33
Hosp1	29
Hosp2	04
Hosp3	09
Male	17
Female	16
Anesthetists MD	03
Obstetricians	04
Specialized anesthetists	06
Nurse anesthetists	20
Median age (years old) (Min: 23–Max: 57)	39.6
Median professional seniority (years) (Min: 1–Max: 22)	7.8

From the data collected in the three hospitals, the indication and the timing of the antibiotic prophylaxis were the criteria that had the best scores: 90.1% and 97.0%, respectively. On the contrary, 69.7%, 48.5%, and 51.5% of the HcPs did not provide good responses to the choice of molecule, dose, or duration of administration of antibiotic prophylaxis, respectively. Only 5 medical doctors out of the 33 participants (15.2%) provided a good response to the five conventional criteria (scored 5/5). The mean level of knowledge was 3.3 out of 5. A total of 25 HcPs (75.8%) scored at least three out of five. The HcPs with certain seniority (more than 10 years) indicated the antibiotics of the kit as those recommended. The younger HcPs often indicated broad-spectrum antibiotics. The participants stated that they had not attended training on antibiotic prophylaxis since they started working, and all of them declared that antibiotic prophylaxis practice has to be improved in their hospital. The levels of the response of the HcPs on the five conventional criteria for antibiotic prophylaxis are represented in Figure 1.

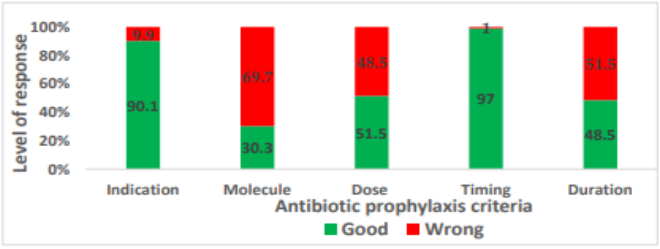

Figure 1. Level of response of the healthcare professionals.

For the three less-known criteria, we calculated the scores of the responses for each socio-professional category, with the results displayed in Table 2. From the analysis of the results, we noticed that the medical doctors (MDs) provided better responses than the

nurses (score out of 5/5: 15.2% of MDs versus 0% of nurses; good dose: 69.2% of MDs versus 40% of nurses; good duration: 76.9% of MDs versus 30% of nurses), and 40% of the nurses did not know the antibiotic recommended for prophylaxis.

Table 2. Repartition of the scores of three criteria less-known according to socio-professional categories.

Criteria		Medical Doctor n = 13 (%)	Nurse n = 20 (%)
Choice of antibiotic	Ampicillin	2 (15.4)	5 (25.0)
	Amoxicillin + clavulanic acid	6 (46.2)	6 (30.0)
	Cefazoline	3 (23.1)	0 (0.0)
	Ceftriaxone	2 (15.4)	1 (5.0)
	Did not know	0 (0.0)	8 (40.0)
Dose	Good	9 (69.2)	8 (40.0)
	Wrong	4 (30.8)	10 (50.0)
Duration	Good	10 (76.9)	6 (30.0)
	Wrong	3 (2.3)	14 (70.0)

2.2. Interviews

The interviews were conducted over two months and included 19 healthcare professionals (9 doctors and 10 nurses; 11 women and 8 men) from the 33 respondents of the previous sample within the three hospitals. The study population ranged from 23 to 57 years in age. Ten face-to-face interviews and two focus groups of three and five participants, composed exclusively of nurse anesthetists, were conducted. All participating medical doctors preferred face-to-face interviews (not focus groups). The discussions lasted approximately 20–45 min for the individual interviews, and 36–50 min for the focus groups. Apart from the field notes of one of the interviewees, no field notes were taken for the recorded interviews. The obstetricians in one of the three hospitals did not give us the opportunity to conduct interviews with them. Data collection was stopped when we did not have other volunteer participants in the study period.

Within the data emerging from the verbatim retranscription, five main determinants subdivided into 17 codes were inductively identified to influence antibiotic prophylaxis achievement in hospitals: patient health determinants, hospital-related determinants, healthcare professionals' individual determinants, central organizational and structural determinants (policy management), and patient behavior determinants. Figure 2 shows the organization of the five determinants of improper antibiotic prophylaxis practices.

2.2.1. Patient Health Determinants

In the opinion of the HcPs, patients' health determinants may influence antibiotic prophylaxis practices in terms of their personal hygiene, medical history, and occurrence of complications after a cesarean section. They also thought that the fact that some patients may already be contaminated with resistant germs has to be considered.

When we asked about the reasons that can lead to the choice of antibiotic for prophylaxis, one of the obstetricians, referring to patients' hygiene and other required hygiene conditions, answered as follows:

> *"But for me, it is above all the patients who do not wash themselves properly- the hygiene of the skin on which we are going to work on. The absence of shower before patients enter in the operating room. The conditions that must be met before the patients enters the operating room are not met."* (Gynecologist Medical Doctor 3, Hospital 2)

On the contrary, a nurse anesthetist argued that patient contraindications (allergies, renal failure, etc.) to the antibiotics in the kit (ampicillin and gentamicin) and the type of CS (emergency vs. planned) can impact HcPs' attitudes toward antibiotic prophylaxis practices.

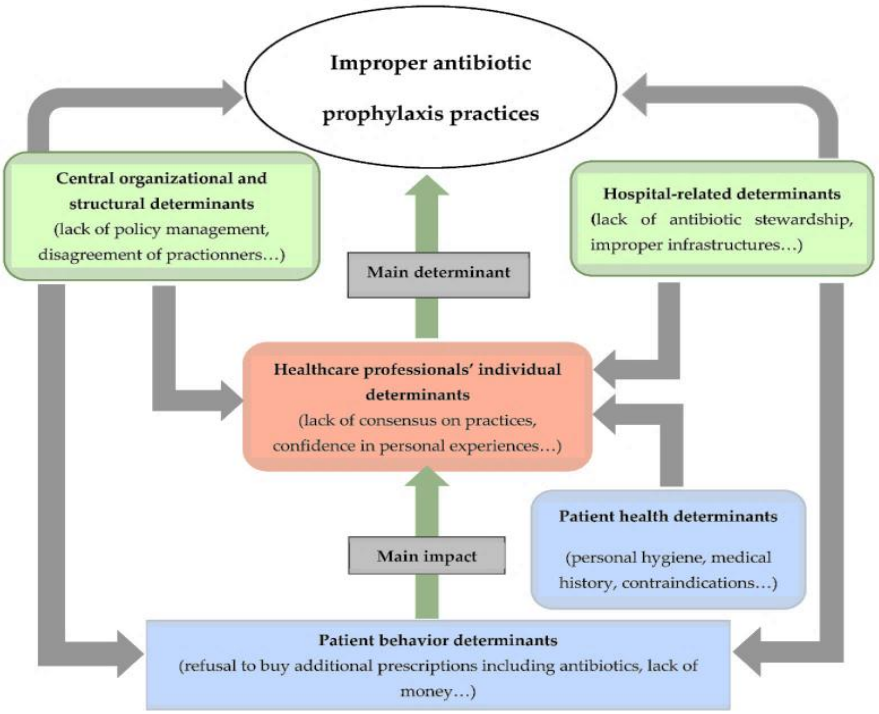

Figure 2. Organization of the five determinants of improper antibiotic prophylaxis practices.

> *"Now, there are some women for whom we do not use gentamicin. But if the woman is not allergic to ampicillin, we will use both."* (Nurse Anesthetist 4, Hospital 1)
>
> *"We systematically administer 2 g of ampicillin and 160 mg of gentamicin if the woman has no history of hypertension."* (Nurse Anesthetist 2, Hospital 3)

In sum, it appears that the perception of safety is key to the choice of antibiotic prophylaxis in terms of the molecule, dose, and duration.

2.2.2. Hospital-Related Determinants

Organization and conditions of care in the hospitals were frequently described as influencing antibiotic prophylaxis practices. Inadequate or inconstant hospital infrastructures with potential consequences for hygiene could influence the achievement of the antibiotic prophylaxis criteria. Then, in the Benin work context, the lack of important tools or an aseptic environment and improper operating rooms were mentioned as reasons for using different antibiotic prophylaxis practices than those recommended. Again, the perceived infectious risk related to contamination of the environment and the global safety of the patient drove the HcPs' behavior.

> *"Yes, the working conditions. To start, the climatic conditions make it impossible to do things differently. And then the surgical units are also substandard—you couldn't say that the unit is systematically sterile."* (Operating Room Nurse, Hospital 2)

The capacity of the hospitals to provide the recommended antibiotics plays an important role in the quality of antibiotic prophylaxis practices. Limited financial and logistical resources induced variable and/or incomplete composition of the CS kit in some hospitals. An interviewee mentioned that the antibiotic provided in the kit is the cheapest, and this choice was made for the form.

> *"But that's what's cheaper, that's why they put that in the kit to free themselves."* (Nurse Anesthetist 2, Hospital 3)

Others suggested that more resources have to be provided to hospitals, since limited resources can lead to an improper antibiotic in the kit, in turn, resulting in improper practice.

> *"We must also think about providing public hospitals with resources. Maybe it's because they don't have the financial means that they do pretty much."* (Nurse Anesthetist 3, Hospital 2)

Regardless of the knowledge of the HcPs on antibiotic prophylaxis or their point of view on the kit, they tended to use what they had available. From the analysis of our data, we understood that, if the contents of the kit provided by the hospital are in line with the recommendations, they will respect the guidance, despite a lack of knowledge or a conflicting point of view on antibiotic prophylaxis. If the antibiotics become available too late, the timing of prophylaxis will not be respected, even when HcPs' knowledge of correct timing is good.

> *"Yes, actually, at a given moment, you use what you have, and that's it. If you see some Ciplox® (ciprofloxacin) in the box, you use it; if at another time, there isn't any, you don't use anything at all."* (Anesthetist Medical Doctor 2, Hospital 1)

Disagreement between specialists, preference for departmental habits over central recommendations, and inactive stewardship policies have led to a lack of consensus in the hospitals, which might lead to different practices within the same hospital.

> *"It's here, in reanimation, that our doctors said, 'No more ampicillin here.' The antibiotic you should use is co-amoxiclav (amoxicillin + clavulanic acid); at least that's what we use. That's not a hospital consensus."* (Nurse Anesthetist 1, Hospital 1)

Communication issues at several levels were linked to the lack of consensus and, more generally, to the use of improper antibiotic prophylaxis:

With hierarchy: HcPs reported that administrative managers did not share the CS kit information with all parties concerned, or they shared it with a delay, so the practices in the hospitals did not conform to central recommendations.

> *"But apparently it was the hospital managers who have left to some workshops; but they didn't give us any feedback."* (Gynecologist Medical Doctor 1, Hospital 2)

Between specialists: Anesthetists and obstetricians working in the same department had different ideas on antibiotic prophylaxis, and did not make decisions or discuss them together to produce a consensual rule.

> *"The gynecologists hold staff meetings every day, and we are invited to the Monday staff meeting. I think the communication methods need to be reviewed because when we say, 'That's what needs to be done,' they come along and do things their way."* (Anesthetist Medical Doctor 1, Hospital 1)

Between colleagues: Practitioners in the same field and in the same hospital had divergent opinions on practices of antibiotic prophylaxis for CSs.

> *"That's why I don't agree completely with my colleague, because she's not aware of what is in the kit and she hasn't been curious enough to ask."* (Gynecologist Medical Doctor 1, Hospital 2)

Across the patient pathway: Taking care of patients is not a global concept. Oral or written information about patients (patient records) are rare or not considered from one department to another. Each department works unilaterally, driving confusion, omissions, and lowering standards in antibiotic prophylaxis practices.

> *"The thing is that here we don't get any more information about the patients. I don't know whether there are infections afterwards because we don't know anything about what happens after day one."* (Anesthetist Medical Doctor 2, Hospital 1)

The interviewees highlighted the low activity of the stewardship policy in their hospitals. They then expressed a veritable need of evidence-based medicine and data to improve their practices. They stated that relevant feedback about the biological tests performed and continuous training on antibiotic use are important to improve antibiotic prophylaxis practices.

> *"No, not that I know; but if there is a structure like that in place and it was never obvious to them before that they should look at how antibiotic prophylaxis is carried out on women, there is something wrong."* (Anesthetist Medical Doctor 2, Hospital 1)

2.2.3. Healthcare Professionals' Individual Determinants

The HcPs' views on the cesarean kit, related to their knowledge about antibiotic prophylaxis and their perception of freedom of practice, influence their practices. The HcPs expressed variable confidence in the kit as far as efficacy is concerned. Knowledge about antibiotic prophylaxis, such as the antimicrobial spectrum required, could help them to understand this.

On the one hand, some healthcare professionals perceived the advantages of having a proper antibiotic prophylaxis policy to save money for patients, avoid antimicrobial resistance, and standardize quality practices.

> *"Respecting that protocol, which, in my opinion, is good and it avoids patients having to make unnecessary expenditures, could even lessen resistance."* (Gynecologist Medical Doctor 1, Hospital 2)

The HcPs appreciated when the contents of the kit allowed antibiotic prophylaxis to be practiced in line with their "*school of thought*" concept.

> *"We do what we have seen others do. You cannot just decide to use a third-generation cephalosporin, for example. That's not in line with what is done."* (Anesthetist Medical Doctor 4, Hospital 1)

On the other hand, some of the HcPs preferred an alternative protocol (antibiotic choice) for antibiotic prophylaxis. The HcPs in certain hospitals had more confidence in their personal experiences.

> *"No, we draw up our own protocol based on what we have experienced in the service."* (Gynecologist Medical Doctor 2, Hospital 3)

Despite their preference for alternative protocols, some practitioners resigned themselves to using the kit.

> *"But none of those molecules are available here in Benin. So, we are resigned to that."* (Anesthetist Medical Doctor 2, Hospital 1)

An interviewee pointed out the overuse of antibiotics in some interventions as follows:

> *"Sometimes, we exaggerate in the antibiotic prophylaxis here. Me, I often have trouble when we want to do clean intervention (for example the planned hernia intervention), and we put Ceftriaxone for prophylaxis."* (Nurse Anesthetist 2, Hospital 3)

Leadership in antibiotic prophylaxis decisions also had an impact on the practices. Some of the HcPs considered the kit as a landmark.

"Antibiotic prophylaxis is based on what's in the kit. We use the antibiotics that are available in the kit." (Gynecologist Medical Doctor 1, Hospital 2)

Other interviewees stated that the doctor's decision is the landmark, and that the other members of the team should abide by it. He or she is free to change what they want to use in their practice, and the doctor is not under any influence.

"In the end, the surgeon (doctor) decides on the antibiotic, which we continue after the surgical unit until the time comes to stop and replace it with oral administration." (Operating Room Nurse, Hospital 2)

"After the intervention, it is the gynecologist who defines whether we should continue the prophylaxis or not and marks it in the post-operative protocol." (Nurse Anesthetist 2, Hospital 3)

Some of the HcPs feel obliged to follow the kit protocol despite their own opinion, whereas others continue to consider what they were taught in their training.

"Except that the ampicillin, we use there, I don't really agree with that. Even if we can go to ceftriaxone, it will be good" (Nurse Anesthetist 3, Hospital 3)

"Because what I was taught about antibiotic prophylaxis when I was in training is that you have to start low and then go up" (Nurse Anesthetist 2, Hospital 3)

2.2.4. Central Organizational and Structural Determinants (Policy Management)

The organization and structure of the CS fee exemption policy in Benin were a matter of controversy. Some disagreements on central policy management were reported in all of the hospitals included in our study. In addition to the perceived inefficacy of the kit, the negative point of view of the HcPs on the national policy might influence the implementation of standardized antibiotic prophylaxis.

"Their kit is useless; when it comes to antibiotic prophylaxis, it's worthless." (Anesthetist Medical Doctor 3, Hospital 1)

A lack of communication or consensus between policymakers and practitioners emerged in the verbatim transcripts. The practitioners felt uninvolved in the policy formulation and were hesitant.

"In my opinion, there was no consultation of local healthcare workers about this business of fees exemption in cesarean. It's a political matter. We were very hesitant at first because the basis for it is not clear." (Anesthetist Medical Doctor 1, Hospital 1)

Low approval of the antibiotics selected in the kit by the central authority, and the absence of monitoring of the utilization of the kit were expressed by the interviewees.

"We have available to us a prepacked kit that includes an antibiotic that is not indicated for prophylaxis." (Anesthetist Medical Doctor 2, Hospital 1)

2.2.5. Patient Behavior Determinants

The interviewees commonly described patient behavior as a central determinant of the poor achievement of antibiotic prophylaxis practice. The HcPs bemoaned the fact that patients do not bring any antibiotics, do not buy the prescribed quantity of antibiotics, or do not bring them on time. Limited resources for patients (lack of money) to buy antibiotics (some or all doses) was frequently mentioned. Patients also frequently misunderstood the retroactive reimbursement for the CS procedure, and, therefore, refused the additional fees for the antibiotic prescription when CSs are supposed to be exempt of user fees. Thus, we can hypothesize that patients' behaviors can influence all of the conventional criteria for antibiotic prophylaxis practices.

"Let me tell you that for some time now, most can no longer manage to pay. They say, 'we can't buy it," and we say, 'go and buy whatever you can.' Sometimes some of them come back with two bottles, others with one bottle." (Nurse Anesthetist 1, Hospital 1)

3. Discussion

Our study assessed the level of knowledge and explored the beliefs of healthcare professionals on antibiotic prophylaxis in CSs in the context of the user fees exemption policy in three hospitals in Benin. The rate of response of the participants to the survey of knowledge according to the five conventional criteria of antibiotic prophylaxis was approximately 94.3%, which is higher than the 84.8% reported in a Saudi study in 2013 [25] , and the 54.7% reported in a Burkinabe study in 2013 [26]. Analysis of the data showed poor scores regarding the knowledge of antibiotic choice, dose administered, and duration of administration. Even if the mean level of knowledge was 3.3 out of 5, we noticed that these three criteria were poorly known and were in line with the results we obtained in a previous observational study [16]. The qualitative data provided some insights to understand the poor practices.

First of all, concerning the choice of antibiotic, the HcPs expressed their disagreement according to the antibiotics selected in the kit, and the CS fee exemption policy in general. Some physicians did not consider the kit safe enough; thus, they were more confident in their own abilities, and preferred to use broad-spectrum antibiotics (contrary to the central recommendation) to avoid the impact of antimicrobial resistance and wound contamination in their patients. In this way, such practices can lead to a vicious cycle of antimicrobial consumption and resistance, as described in a Hungarian study [27]. Moreover, Baadani et al. reported that confidence in one's prescribing abilities while not recognizing the importance of the guidelines suggests that some physicians may be oblivious to their shortcomings [25]. Echoing our data, 69.1% of respondents in a knowledge survey performed in Burkina Faso declared the use of third-generation cephalosporin in prophylaxis [26]. However, the kit imposes a framework of practices, and some of the HcPs obeyed this, despite their thoughts. Nevertheless, the other HcPs were pleased with the use of the kit, and perceived the use of its antibiotics as a way to improve patient safety and control costs. Moreover, the use of the antibiotic prophylaxis kit resulted in improved conformity of practices with recommendations [21] . The use of a standardized kit supported by strong statements, the hospitals' management, and the antibiotic stewardship team could help to fix the lack of communication, and provide a consensus within hospitals. The HcPs were looking for some monitoring of infections and evidence-based practices. In some cases, the HcPs adopted a pragmatic, if not resigned, point of view on antibiotic prophylaxis, and used what was available (in the kit or brought by the patients), regardless of their knowledge or preference. Indeed, compliance with antibiotic prophylaxis guidelines depends not only on the physician's prescription, but also on the availability of the antibiotics in the hospitals, as well as on what the patient can buy and bring in time. In many cases, the patient is expected to buy their antibiotics, but this instruction is not completed due to various reasons.

Second, according to the statements of the interviewees, an improper dose of antibiotic prophylaxis is due to the patients' behaviors in terms of refusal to buy antibiotics or buying incomplete doses. Curiously, the HcPs' level of knowledge was also low for this criterion. Thus, we think that the HcPs were less aware of good practices of antibiotic prophylaxis; otherwise, they could coach the patients to provide the correct dose of antibiotics for prophylaxis. Therefore, we can hypothesize that there is a relationship between the level of knowledge and practices. However, in another study, a dissonance was found wherein participants could correctly identify the appropriate use of antibiotics, and yet fail to apply them in practice [28]. Adherence to guidelines for antibiotic prophylaxis remains a challenge, since a previous systematic review observed a significant variation in the outcomes of all of the antibiotic prophylaxis criteria [29] .

Third, improper duration can be explained by the fact that the HcPs fear the occurrence of infection after a CS because of the inadequate hospital environment, the patient's hygiene, and the lack of an evidence-based protocol. In a study performed in Thailand in 2003, an obstetrician argued that post-operative infections affect his reputation, so he tends to overuse antibiotic prophylaxis [30]. In fact, patient hygiene was reported to be an

important factor that leads to improper use of antibiotics, especially in low-income countries such as Benin, as women have a suboptimal health status, including a lack of hygiene [22].

In sum, from the analysis of the five determinants, we understand that improper practices can be explained by various reasons at different levels, such as a poor level of knowledge among healthcare professionals on antibiotic prophylaxis and a lack of confidence in the antibiotics in the kit, or the unavailability of infrastructure and financial resources for the adequate achievement of antibiotic prophylaxis and the non-conforming implementation of the policy at the hospital level. At the central level, we found that poor management of the policy, in terms of a lack of communication with local HcPs to ensure their adherence to the policy and to consider their opinions on the choice of antibiotics, contributed to the dysfunctions. It results that the failure of the organization of the policy at these three levels often shifts the responsibility of adequate antibiotic prophylaxis to the patient (or their parents). Even if patients are important members of the healthcare team and participate more in healthcare decision-making [31], they are not skilled in healthcare and cannot understand and weigh the importance of prophylaxis. It becomes essential for policymakers and healthcare professionals to adequately play their roles to ensure patient safety.

This mixed-methods study is the first to assess the level of knowledge and beliefs on antibiotic prophylaxis in CSs in Benin. The survey, combined with qualitative data, helped to understand the link between knowledge and beliefs on the one hand, and their effects on antibiotic prophylaxis practices on the other hand.

This study has some limitations. First, the sample of the survey was small. This was due to the challenge we faced to enroll participants in the study, mostly because we opted to administer the question only on the day we reached the hospital, and to collect the filled questionnaires within a short deadline. Second, all of the included healthcare professionals were from hospitals located in the southern part of the country; thus, they are not entirely representative of the whole country. It will be interesting to perform a large study including other hospitals and more healthcare professionals. Third, in the qualitative study, we did not reach saturation, because some HcPs did not accept being interviewed. However, we think our findings could contribute to improvements, since they have helped to understand that the poor achievement of antibiotic prophylaxis practices according to the five conventional criteria is due to the low level of knowledge and poor management of the policy.

4. Materials and Methods

This mixed-methods study encompassed quantitative and qualitative data to assess the level of knowledge and explore beliefs on antibiotic prophylaxis practices in hospitals. After a survey, some interviews were conducted with healthcare professionals. From August to October 2017, through a convergent parallel design study [32], we collected data on the knowledge and beliefs on antibiotic prophylaxis of HcPs in three representative hospitals chosen based on the three levels of the healthcare system in Benin (one national teaching hospital: hosp1; one zonal teaching hospital: hosp2; one confessional private hospital: hosp3). Moreover, in our previous study , we noticed that antibiotic practices are different between the three hospitals [16]. Thus, performing qualitative studies in each kind of hospital can help to determine the challenges faced in these different settings. Quantitative data on the level of knowledge of antibiotics were collected through a survey using a self-administered questionnaire (File S1), whereas qualitative data were gathered through face-to-face interviews and focus groups performed with groups of at least two HcPs with an interview guide (File S2), as described below. All data collection tools were in French, and data collection was conducted in French also.

4.1. Assessment of the Level of Knowledge of Antibiotic Prophylaxis

The HcPs who were in the obstetric ward at the time we reached the hospital were informed about the purpose of the study, and the self-administered questionnaire, adapted from those used in a similar study in Burkina Faso [26], was given to those that agreed to participate in the survey (obstetricians, anesthetists, and nurse anesthetists). It comprised 10 multiple-choice questions in order to assess the knowledge of the antibiotic prophylaxis concept and its five conventional criteria (indication, choice of the molecule (ampicillin alone or + gentamicin and/or metronidazole from the kit or cefazoline), dose of antibiotic (double of the usual adult dose), timing (30–60 min before incision), and duration of administration (single administration)) [17].

4.2. Interviews

The face-to-face interviews and focus groups were performed in the three hospitals using a semi-structured guide. The HcPs concerned by antibiotic prophylaxis practices in each hospital (anesthetists, specialized anesthetists, nurse anesthetists, and obstetricians) were recruited based on convenience sampling. Depending on the availability of the HcPs, focus groups or face-to-face interviews were organized by physical contact at the sites (wards). The meetings were conducted by the principal investigator of the study (a female external hospital pharmacist and PhD student), who was trained to perform qualitative research. She met the HcPs previously during the observational study conducted in 2016 [16] . The interview guide was open-ended and explored the HcPs' habits of antibiotic prophylaxis, perceived performance, and issues related to it. The guide was updated after the first interviews, where necessary. After obtaining authorization from the interviewees, the interviews were recorded using the dictaphone of two mobile phones. One of the interviewees did not consent to be recorded, so we then made field notes during the interview.

4.3. Data Management and Analysis

Quantitative data were analyzed using IBM Corp (released 2016; IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp). Descriptive statistics presented continuous variables using medians, and categorical variables were presented as numbers and percentages. The filled questionnaires were scored on a basis of five points considering the five conventional criteria. One point was attributed to each conventional criterion with a good response, and 0 points for a wrong response. The score of each health professional was calculated by summing the points obtained for the five criteria. Each HcP's knowledge was scored as x/5 (x = total of the points gathered). The mean level of knowledge was calculated by pooling the scores of all participants and dividing the sum by 33. Since the five conventional criteria are essential for the quality of antibiotic prophylaxis, we applied the "all-or-none" law to categorize the level of knowledge of the HcPs. Thus, the level was considered as good when the score was 5/5. Any other score below 5/5 was considered as poor.

In addition, we asked an open question about practice improvement and demographic characteristics (age, gender, qualification, and professional seniority). The completed questionnaires were picked up on the day of the survey or a few days later, according to the HcPs' availability. All of the collected data were anonymously registered.

All of the collected data were transcribed verbatim in Word software. Each file was named using the words "interview or focus group + the name of the hospital."

Data analysis was performed by two pharmacists from different countries, including the main investigator. Both were aware of the Benin context, and the main investigator was from Benin. The analysis was performed using inductive content analysis methods—specifically, a "manifest analysis," in which we stood on "what the interviewees have been said" without straying from our research questions. The analysis comprised approximately five steps, described following a process drawn by Bengtsson [33]. One additional

step was used in our case (Decontextualization 2). The steps are summarized in Table S1 in Supplementary Materials. The validity of the analysis was based on the triangulation of information between the survey and the interviews, and the coding process which helped to identify the similarities and differences in the interviewees' perceptions. Rigor and quality assurance of our study are described in Table S2.

5. Conclusions

Cesarean sections can be a life-saving intervention, and antibiotic prophylaxis is an uncontestable parameter to ensure the quality of life and health of patients. Unfortunately, its criteria are insufficiently known by the HcPs in Benin. The lack of confidence in the kit's antibiotics, the absence of consensus between healthcare professionals, and their disagreement with the national policy were noticed in the hospitals included in our study. This results in failure in the implementation of the policy, and imposes additional fees for patients, despite the user fee exemption for cesarean sections. The healthcare professionals recognized that their practices were not optimal, and attested that they required an operational antibiotics stewardship policy in their hospitals in order to improve said practices. Several determinants involving all actors, implemented on all levels of the healthcare system in Benin, could help to address the challenges of good practices in order to decrease the occurrence of antimicrobial resistance and ensure women's safety.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/antibiotics11070872/s1. Table S1. Steps of data analysis. Table S2. Rigor and quality assurance. File S1. Questionnaire of assessment of the level of healthcare professionals. File S2. Semi-structured interview guide

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CHAPTER 3: Assessment of supply chain and quality of injectable antibiotics in Benin.

Chapter 3 overview

This chapter displays the results of data collected in the six hospitals partner of the MUST-TIC project. The results were about:

- the audit of the supply chain and the availability of antibiotics used in surgical prophylaxis (obstetric and digestive) in hospitals pharmacies through a master's degree research at Université d'Abomey Calavi (Appendix 1).
- the assessment of the chemical quality of injectable antibiotics used in prophylaxis (obstetric and digestive) through a master's degree research at Université d'Abomey Calavi, Bénin.

Background

- Substandard and falsified medicines are an enormous threat to global health.
- In low and middle-income countries, the impact of Substandard and falsified medicines is high with consequences such as failure of treatment, antimicrobial resistance, and death.
- Antibiotics are the most frequently falsified medicines, accounting for 28% of global falsified medicines.

Inputs from this chapter

- The availability of injectable antibiotics for prophylaxis was poor in the six hospitals and the supply chain was poorly performant.
- A total of 85% of samples passed all the tests' quality. The remaining 15% failed visual inspection and active ingredient quantification tests.
- In the context of limited resources, this study showed that routine laboratory controls are feasible through the development of simple and less expensive methods than those described in the pharmacopeia.

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Assessment of the Quality of Injectable Antibiotics in Benin

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Abstract. Substandard and falsified medicines are an enormous threat to global health. Poor quality antibiotic preparations contribute to the development of antimicrobial resistance. In surgery, where the occurrence of healthcare-associated infections is high, healthcare teams need to rely on the quality of antibiotic prophylaxis to prevent infections. We assessed the quality of antibiotics used for surgical infection prophylaxis in Benin. Thirty-three samples were collected from six hospitals located in various departments in Benin. The antibiotics (powders for injection: amoxicillin + clavulanic acid, ampicillin, ceftriaxone; solutions for injection: ciprofloxacin, gentamicin, metronidazole) were assessed using visual inspection, pharmacotechnical tests (including uniformity of mass, pH measure, sterility test, and active pharmaceutical ingredient identification), and assay tests (including a simple analytical method thin layer chromatography) and complex analytical techniques (ultraviolet-visible spectrophotometry, high-performance liquid chromatography—diode-array detection, conductometry). Because the material needed for the methods recommended by the pharmacopeias to assess the dosage of gentamicin was not available, we developed and validated a conductometry method. Results showed that 97% ($n = 32$) of the samples passed visual inspection; 100% ($n = 33$) of the samples passed the pharmacotechnical tests, identification of active ingredients, and sterility test; 88% ($n = 29$) passed the test for percentage of active pharmaceutical ingredients. Overall, 15% of the samples did not pass the quality test (3% on visual inspection and 12% for excess active ingredients). Although most of the samples passed the quality tests, it appears important to perform routine quality control for intravenous medicines.

INTRODUCTION

Medications are important products for disease prevention and control in the healthcare system. In addition to cost, availability, and appropriate use, quality is essential for their effectiveness. Medication quality is a challenge in all countries because of substandard and falsified (SF) medicines. Ensuring equitable access to quality pharmaceuticals is thus a key development challenge and an essential component of health-system strengthening and primary healthcare reform programs worldwide.[1]

Substandard medicines, also called "out of specification," are defined as "authorized medical products that fail to meet either their quality standards or their specifications, or both."[2] Medicines may be substandard as a result of poor manufacturing practices, unsuitable packaging, or inappropriate transport or storage conditions.

Falsified medicines, also called counterfeit medicines, are defined as "medical products that deliberately or fraudulently misrepresent their identity, composition, or source."[2] SF medicines are a threat for health, and every part of the world is concerned to different degrees. The proportion of SF medicines has been estimated at less than 1% in industrialized countries, and 10% to 30% in low incomes countries.[3]

After the Bamako initiative in 1987, access to medicines in sub-Saharan African countries has improved,[4] but SF medicines have frequently been reported.[5] Since 2013, the WHO has received 1,500 reports of SF medical products, 42% of which were from the WHO African region.[2]

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In low- and middle-income countries, the impact of SF medicines is high, involving 10% of all medicines, with an economic cost of US $10 billion to $200 billion.[6] SF medicines may cause prolonged illness or disease and treatment failure and can also directly harm patients through toxic effects or adverse reactions and sometimes death.[7–9]

Antibiotics are the most frequently falsified medicines, accounting for 28% of global falsified medicines and representing 5% of the global antibiotic market. Of all falsified medicines, 17% are injectable formulations.[3] Poor-quality antibiotic preparations contribute to the development of microbial resistance to antibiotics and to death.[10] Poor-quality antibiotics have been reported in Africa,[11] including cases of substandard injectable ceftriaxone in Uganda with fatal consequences[12] and cases in Kenya.[13] The evolution of antimicrobial resistance is a major risk from poor-quality drugs because of microbial selection and geographic spread.[5] The United Nations, in its N° 3.8 Sustainable Development Goal, includes access to safe, quality, and affordable medicines to reduce the threat from SF medicines.[14]

The effectiveness of antibiotics is essential in infection prevention and control, which is a key feature in all healthcare departments especially in surgery, where the occurrence of infections, notably healthcare-associated infections, is high.[15] Infection prevention and control occupies a unique position in the field of patient safety and quality universal health coverage, because it is relevant to health workers and patients at every single healthcare encounter. One of the core components of infection prevention and control is good management of antibiotic use by both oral and injectable routes.[16]

In Benin, antibiotics are the second most commonly used therapeutic class after antimalarials.[17] Numerous studies have reported poor-quality antimalarials in Benin.[18–20] Assessing the quality of antibiotics can help ensure their effectiveness

and contribute to reducing the evolution of antimicrobial resistance.

Given the importance of the quality of antibiotics in surgical infection prophylaxis,[21] we assessed the quality of intravenous antibiotics (powders for injection of amoxicillin/clavulanic acid, ampicillin, and ceftriaxone; solutions for injection of ciprofloxacin, gentamicin, and metronidazole) frequently used for surgical infection prophylaxis in Benin.

MATERIALS AND METHODS

Materials and instrumentation. This research was conducted in the frame of a multidisciplinary project involving six hospitals in Benin. Antibiotic drugs were purchased in pharmacies located in the six hospitals in the south of Benin: Centre National Hospitalo-Universitaire Hubert Koutoukou Maga (CHNU-HKM, Cotonou), Centre Hospitalo-Universitaire de la Mère et de l'Enfant Lagune (CHU-MEL, Cotonou), Centre Hospitalo-Universitaire Départemental Ouémé-Plateau (CHUD-OP, Porto-Novo), Centre Hospitalo-Universitaire de Zone Suru Léré (CHUZ Suru-Léré), Centre Hospitalo-Universitaire de Zone d'Abomey-Calavi/Sô-Ava (CHUZ-AC/SA, Abomey Calavi), and Hôpital Bethesda (Cotonou). The hospitals are from various levels of the healthcare system and for anonymity are simply named "hospital 1" through "hospital 6" in this report.

We studied the six antibiotics frequently used in surgical infection prophylaxis as reported in a Beninese study[22] and other unpublished data: amoxicillin + clavulanic acid (J01CR02), ampicillin (J01CA01), ceftriaxone (J01DD04), ciprofloxacin (J01MA02), gentamicin (J01GB03), and metronidazole (J01XD01). The antibiotics were brand or generic forms from different manufacturers. For easy handling, the antibiotics were coded using alphabetical letters and the number of each hospital (e.g., A1 for amoxicillin + clavulanic acid from hospital 1).

We planned to collect 36 samples (the six antibiotics from the six hospitals), with each sample composed of 30 vials of the same batch of antibiotic to have sufficient for all the analyses. We therefore aimed to collect: six samples of amoxicillin + clavulanic acid powder for injection, six samples of ampicillin powder for injection, six samples of ceftriaxone powder for injection, six samples of ciprofloxacin injection, six samples of gentamicin injection, and six samples of metronidazole injection, giving a total of 1,080 vials for analysis.

An adapted form from the WHO was used to record the visual inspection information.[23] The form includes about 57 items divided into four categories (secondary packaging, primary packaging, medication leaflet, physical appearance of power or injection solution) (see Supplemental materials, Appendix 1).

The following reagents were used for high-performance liquid chromatography (HPLC):

- acetonitrile (HPLC grade) purchased from Fisher Scientific (Loughborough, United Kingdom),
- potassium dihydrogen phosphate, sodium dihydrogen orthophosphate monohydrate from VWR chemicals (Brussels, Belgium),
- acetic acid (99.8%) purchased from BDH AnalaR (London, United Kingdom),
- methanol (HPLC grade) from Honeywell (Brussels, Belgium),
- phosphoric acid (100%) from Certa (Braine-l'Alleud, Belgium),
- triethylamine from Surechem products Ltd (Ipswich, United Kingdom), and
- ultrapure water obtained locally using a PURELAB CHORUS water purification system from VEOLIA (Paris, France).

Chemical reference substances (U.S. Pharmacopeia [USP] grade) of amoxicillin (86.9%), ampicillin (99%), ceftriaxone (92.6%), ciprofloxacin (99.6%), gentamicin sulphate (67.1%), and metronidazole (100%) were purchased from the USP (Rockville, MD); clavulanic acid (100%) was purchased from Sigma Aldrich (Darmstadt, Germany).

Qualitative analyses were performed with HPLC equipment from Hitachi VWR (Brussels, Belgium), controlled using the Chromaster System Manager version 1.1 (VWR; Brussels, Belgium) and a separation module coupled to the Hitachi photodiode array (PDA) detector (VWR); an ultraviolet-visible spectrophotometer (UV-VIS Spectrophotometer 6300PC VWR; 634-6041 series); and thin layer chromatography plates (TLC Silica gel 60 F_{254}, Merk Darmstadt, Germany). Quantitative analyses were carried out using HPLC, the UV-VIS spectrophotometer, and a conductometer (WTW Cond 3210, No. 13071009, Weilheim in Oberbayern, Germany).

pH values were measured using a pH meter (pHenomenal, pH1000H, Ser. No. 13150774, VWR), accuracy ± 0.1 pH.

The well-characterized microbial strains *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Bacillus spizizenii* ATCC 6633, *Clostridium sporogenes* ATCC 19404, *Candida albicans* ATCC 10231, and *Aspergillus brasiliensis* ATCC 16404, purchased from Medimark Europe (Grenoble, France), were used for the sterility test. The thioglycollate broth was purchased from MERCK (Darmstadt, Germany), the casein and soy hydrolysate liquid medium (tryptone soya broth) from HiMEDIA (Mumbai, India), and peptone water from OXOID (Basingstoke Hampshire, United Kingdom).

Two Memmert (Schwabach, Germany) bacteriological incubators, a Touchclave-R (Oldham, United Kingdom) autoclave, and a Telstar (Terrassa, Spain) laminar flow hood were used for all the tests.

Methods. Each sample was accompanied by a sheet detailing the date and location of the collection, the quantity taken, and the conditions of storage (laboratory temperature). Visual inspection and pharmacotechnical tests were conducted at the Laboratoire de Chimie Analytique et Analyse des Médicaments (LCAM) of the Faculté des Sciences de la Santé (FSS) in Cotonou, Benin. The sterility tests were performed in the national laboratory (Agence Nationale de Contrôle de Qualité des produits de santé et de l'eau, ANCQ) at the Ministry of Health (Cotonou, Benin). Samples were collected from the hospitals from December 20 to 27, 2019, and analyses were conducted from January 3 to August 31, 2020.

Each sample was screened using the form mentioned earlier (see supplemental materials, Appendix 1). A medicine was defined as poor quality when it did not conform to at least one of the items on the list. To identify potential poor quality, we recorded information including integrity, expiration date, batch number, and identifying elements on the primary and secondary packaging; information including indications, contraindications, and side effects on the medication leaflet; and physical appearance, such as color, appreciation of clarity for injection solutions, appreciation of granulometry for powder forms, and odor.

A mass uniformity test was performed for powdered samples (amoxicillin + clavulanic acid, ampicillin, ceftriaxone),

realized with 10 vials taken at random from each sample and weighed individually.

An extractable volume test was done for liquid samples (ciprofloxacin, gentamicin, metronidazole). According to European pharmacopoeia, one bottle of ciprofloxacin, one of metronidazole (100 mL), and five vials of gentamicin (2 mL) were poured in different named test tubes and the volumes were read for each of them.

The pH was measured on reconstituted solutions from dissolved antibiotics powders and from antibiotics for injection as recommended by the USP. Acceptability criteria were those of the USP[24] (amoxicillin + clavulanic acid 5.0–9.0; ampicillin 8.0–10.0; ceftriaxone 6.0–8.0; ciprofloxacin 3.5–4.6; metronidazole 4.5–7.0; gentamicin 3.5–5.5).

The tests used for identification and quantification are summarized in Supplemental Table 1. We used the most common, generic, and validated analytical methods (i.e., UV-VIS spectrophotometry, HPLC-diode array detection [DAD]) described in the literature and pharmacopoeia for five of the six antibiotics: amoxicillin + clavulanic acid, ampicillin, ceftriaxone, ciprofloxacin, metronidazole. The identification and quantitative dosage of gentamicin as described in the pharmacopoeias and the literature consulted (microbiologic titration, molecule derivatization) appeared more complex and required expensive reagents and sophisticated equipment not available in Benin. We therefore used TLC to identify gentamicin and then used a validated conductometry method for gentamicin quantification.

UV-VIS spectrophotometry was used to identify ceftriaxone by comparing the UV spectra of the samples to those of reference standard. This test used the method described by Muhindo et al.[25] See supplemental material, "Methods."

UV spectrophotometric identification was performed by recording and comparing the absorption spectra from the reference and sample test solutions acquired in the range between 200 and 400 nm.

The remaining molecules (amoxicillin, ampicillin, ciprofloxacin, clavulanic acid, metronidazole) were identified using HPLC-DAD and UV-VIS spectrophotometry.

The gentamicin samples underwent identification using TLC. The test solutions and the reference solution of gentamicin sulphate (USP) were prepared in ultrapure water to obtain a concentration of 1 mg/mL (see supplementary material, section "Methods"). Gentamicin was identified by comparing the frontal ratios (Rf) and the spots of the samples to those of the reference.

Quantitative analyses of active pharmaceutical ingredients (API) were carried out using HPLC-DAD, UV-VIS spectrophotometry, and conductometry.

The test sample solution of ceftriaxone prepared according to the method of Muhindo et al.[25] was placed in a cuvet and submitted to a wavelength of maximal absorption of ceftriaxone (240 nm). Three assays were done on each sample. The mean values for the absorbances of the sample and for the chemical reference substance (CRS) solutions were used to calculate the percentage of active ingredient.

The test sample solutions for amoxicillin + clavulanic acid were prepared following the method of Durga et al.,[26] and the test sample solutions for ampicillin, metronidazole, and ciprofloxacin were prepared according to the USP.[24] See detail in supplemental material, "Methods."

HPLC analyses were carried out for amoxicillin and clavulanic acid. USP methods, with a few adaptations, were used for metronidazole, ampicillin, and ciprofloxacin as described in Supplemental Table 2. The chromatographic separation was done in isocratic elution mode. All the data were analyzed according to USP specifications.[24]

Conductometry methods were validated before analyzing the samples of gentamicin. A stock solution of calibration standard (CS) of gentamicin (CRS, 1,000 μg/mL) and sample solutions were prepared based on a method adapted from that described in the literature for aminosides[27] (see detail in supplemental material, "Methods"). Three assays were made for each sample by measuring the conductance of each solution with the conductometer. The mean values of the conductance for the sample solutions and the CRS solution were used to calculate the percentage of the active ingredient (% PA) as described in the supplemental materials. The acceptance limit was 90% to 125% according to the USP recommendation.[24]

We considered the validation criteria commonly used in analytical procedures set out in document Q2 (R1) of the International Conference on Harmonization[28]—namely, selectivity/specificity, trueness, precision (repeatability and intermediate precision), accuracy, linearity, limit of detection, and limit of quantitation (see details in supplemental materials). The acceptance limit was set at ±10% according to the International Pharmacopeia (3rd edition, 2003) and considering consumer risk and the intended use of the analytical procedure. The selected calibration model was linear regression because of its high accuracy index (between −5 and +5) and ease of routine use. The concentration results were back-calculated using the calibration curves. These concentrations were used to determine the relative bias, the precision (repeatability and intermediate precision), the β-expectation tolerance intervals at 95% probability level, and the linearity. Validation calculations were performed using e-noval version 3.0 (Pharmalex S.A, Mont-Saint Guibert, Belgium).

Sterility testing of an injectable medication is a decisive criterion contributing to drug safety. The method for culturing microorganisms to test for product sterility has existed since approximately 1930 [Cleanroom technology, 2015, 1] and involves either filtration of the pharmaceutical product (preferred method according to the European pharmacopoeia), or direct transfer of the product into a liquid culture medium. Because of the material available, we opted for direct transfer of the product into a liquid culture medium.[29] The sterility test was performed in a controlled environment under aseptic conditions [Cleanroom technology, 2015, 1]. To ensure that measures taken to prevent contamination of the critical area did not affect the growth of any microorganism present in samples undergoing sterility testing, we used positive and negative controls for each test.

The validation test for the method was performed before the sterility test to inhibit antimicrobial activity. For this, a typical inhibitor medium and a stock solution of each sample were prepared (see supplemental material).

Because the microorganisms (Supplemental Table 3) used can cause severe disease in humans and constitute a danger for directly exposed employees, we wore protective gloves when handling them and worked in class III biosafety cabinets (TELSTAR, Terrassa, Spain).

For noncompliant samples, similar cases would be looked for in the literature and a report made to the Benin medicines' regulatory agency (Agence Béninoise de Régulation Pharmaceutique, https://www.abrp.bj/) as per usual procedures.

RESULTS AND DISCUSSION

In our study, we collected 33 of the planned 36 samples in the formal supply chain. The sample size was about 990 vials of the 1,080 expected, giving a collection rate of 91.7%. Details of the sample are summarized in Supplemental Table 4. At least one of these three molecules (ceftriaxone, gentamicin, metronidazole) were out of stock in three hospitals, indicating incomplete availability of the antibiotics. This incomplete availability is similar to that observed in a study performed in Cameroon and the Democratic Republic of Congo.[11] This situation can cause delay in initiating antibiotic prophylaxis, resulting in reduced effectiveness.

For the following analyses, the results for each product are expressed in terms of nonconformity—that is, a specified requirement not being fulfilled.[30]

None of the samples had expired on the date of purchase, showing good storage management practices at the hospitals of our study. No irregularities were noticed in physical appearance. Visual inspection showed 97% ($N = 32$) conformity and 3% ($N = 1$) nonconformity. This nonconformity concerned the medication leaflet, which did not have the heading "Drug interactions" and was not translated into French as recommended. This finding indicates nonrespect of good manufacturing practices and lack of care by the provider during the supply process. This rate of nonconformity was higher than that reported in a Senegalese study (0%).[31] Contrary to our findings, nonconformity of several indicators of quality has often been reported,[9,11,32] which has a major impact on the quality of the medicine.

All the samples (100%, $N = 33$) met the European Pharmacopeia (8th edition) requirements for extractable volume and mass uniformity. When weighed individually, the deviation of the individual masses from the average mass did not exceed 10%, and the pH values were within USP specifications. Nonconformity for uniformity of mass results from poor mixing during manufacture but can also be due to uneven distribution of the powder in containers. Nonconformity for uniformity of mass or extractable volume affects the quantity of active ingredient contained in the drugs. The results from this analysis are consistent with the samples having been made using good manufacturing practices and also demonstrate good supply chain practices and good storage conditions in the formal supply chain in Benin.

For all the samples tested, 88% ($n = 29$) passed the tests for the API dosage and 12% ($N = 4$) did not.

Ceftriaxone samples collected in hospitals C1, C3, C4, C5, and C6 had spectra that stacked perfectly with the CSR spectrum. The antibiotics available in these hospitals thus contained ceftriaxone as indicated.

The frontal ratios (0.4), color, intensity, and size of spots of the five samples of gentamicin for injection (E1, E2, E3, E4, E6) were the same as those of the CRS. The antibiotics collected in these hospitals thus contained gentamicin as claimed.

As shown on the chromatogram in Figure 1, the retention time of chemical reference substances matched the major peak in the samples.

On the multi-chromatogram in Figure 2, the first set consisted of six samples, coded A1, A2, A3, A4, A5, A6, claiming to contain a fixed dose of amoxicillin and clavulanic acid (1 g/0.2 g); the second set consisted of six samples coded B1, B2, B3, B4, B5, and B6 and contained ampicillin 1 g; the third set consisted of six samples coded D1, D2, D3, D4, D5, and D6, and contained ciprofloxacin 0.2 g; the fourth set coded F1, F2, F3, F4, and F5 contained metronidazole 0.5 g.

Supplemental Table 5 summarizes the results of the content analyses. All the batches of ampicillin, ciprofloxacin, metronidazole, and ceftriaxone were close to the labeled amounts and within specifications. However, the API contents for amoxicillin and clavulanic acid showed mixed trends. The trends of samples A2 to A6 were all within the same range, whereas the content in A1 had a higher value (114.8% ± 0.6) for amoxicillin than specified and a lower value for clavulanic acid (95.8% ± 0.6). This sample was the only one with a different trademark among the six collected, which may explain the observed result.

For ampicillin, there was a trend to less than 100% content for all samples and for ceftriaxone a trend greater than 100%, with some standard deviations greater than 1. For ciprofloxacin and metronidazole, the API trends were also mixed but in the same range. It is important to highlight that some of the standard deviations were greater than 1 and 2, but this has no significant importance.

Validation of the method to assay gentamicin gave the following results. Supplemental Table 6 (see supplemental material online), we presented the most appropriate selected regression models, sorted according to the accuracy index. The accuracy profiles for gentamicin are given in Figure 3, and the validation criteria are summarized in Supplemental Table 7, where:

- trueness was expressed in terms of absolute bias (in micrograms per milliliter) or relative bias (%) at each concentration level of the validation standards. The trueness of the developed method was good with absolute and relative biases $< 1.8\%$.
- precision was expressed in terms of relative standard deviation values for repeatability and for intermediate precision and did not exceed 2.2%. This indicates good precision of the developed method.
- the linearity of an analytical method is the ability to obtain results directly proportional to the concentration (quantity) of the analyte in the sample within a definitive range. Good linearity was observed between the results (here back-calculated concentrations) and the introduced concentrations, with excellent determination coefficient (R^2 of 0.9995; Supplemental Table 7). The accuracy of the method was therefore demonstrated also by assessing the accuracy profile (Figure 3) for which the relative β-expectation tolerance intervals were within a range of −1.8 to 4.8%, and the relative expanded uncertainly was $< 4.8\%$.

Because the lower and upper tolerance bounds were within the acceptance limits for all the targeted concentration levels, each future result will fall within the acceptance range with a probability of at least 95%.[33] The dosing range is the interval between the lower and the upper limits where the procedure achieved adequate accuracy; dosing ranges were 30 to 90 μg/mL.

The validated method was then used to determine the content of API in the samples of gentamicin injection (E1, E2, E3, E4, and E6). The results obtained for the analyses, consisting of the mean percentage of claimed nominal content and the standard deviation computed on three independent samples (Supplemental Table 8). The gentamicin contents in the

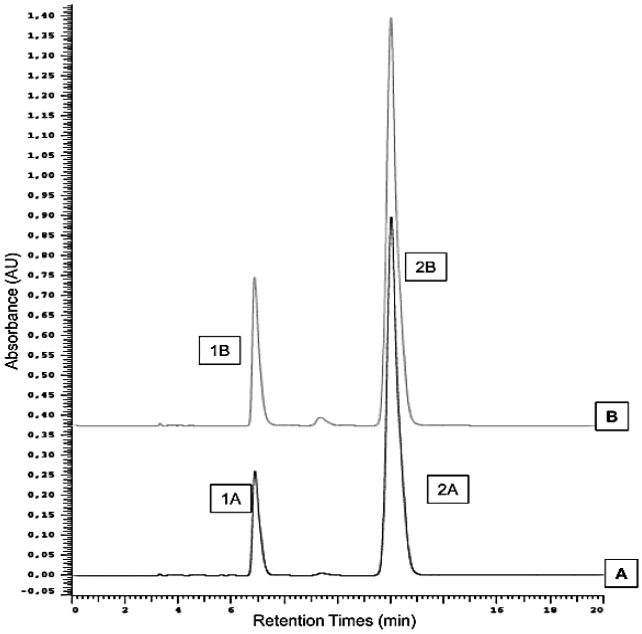

FIGURE 1. Typical chromatograms of amoxicillin and clavulanic acid chromatographic pics of clavulanic acid (**1A**) and amoxicillin (**2A**) in reference solution at 220 nm. Chromatographic pics of clavulanic acid (**1B**) and amoxicillin (**2B**) in sample solution coded E1 at 220 nm. This figure appears in color at www.ajtmh.org.

injection samples were within 124.7% to 126.5%. Four of the samples (E1, E2, E4, and E6) were out of the specification ranges, which can imply a risk of overdosage for the patient. Considering the risk of gentamicin ototoxicity and nephrotoxicity, particular attention must be paid to this product content. Especially that the hospitals do not perform the monitoring pharmaco-therapeutic in patients under gentamicin.

In view of the results, all the samples trended toward higher values. Only one sample (E3) was within the specifications. Curiously, this sample had the same manufacturer as samples E2 and E4 but a different distributor. We do not think that this difference could have an impact on the product. Moreover, falsified medicines usually have low quantities of API to make more profit.

The method applied is simple, fast, robust, easy to perform, and does not require large equipment; thus, it is well suited for routine checks. However, it is not very selective because all the ions present in the analyzed medium can interfere with the process. This factor may explain the risks of excessive doses observed during the application of the method. It could be relevant to combine a separation method (HPLC) with a conductivity detector.

After the third day for bacteria and the fifth day for fungi, no turbidity was noticed in the culture mediums, indicating the absence of growth of microorganisms. All the samples (100%, $N = 33$) met this requirement. We can conclude that the antibiotics available for prophylaxis in the hospitals did not represent a risk of contamination for patients.

In summary, most of our samples were conform (Supplemental Table 9), probably because our samples were taken from the formal supply chain. Other studies in less formal settings in developing countries reported contrasting findings.[9,34] It is likely that the good quality of the antibiotics available in the included hospitals is linked to easy access to legal providers of medicines and to the locations of the hospitals in southern Benin, where they are within range of the regulatory authorities. Furthermore, the repression operation, Operation PANGEA IX, which attempts to curtail the use of medicines from the informal supply chain, may also have had an impact.[35] Nevertheless, oral forms of antibiotics are often nonconform,[9,11,32] likely because oral forms are more widely used, their manufacture does not require many resources, and, in contrast to injectable forms, a qualified person is not needed for their use.

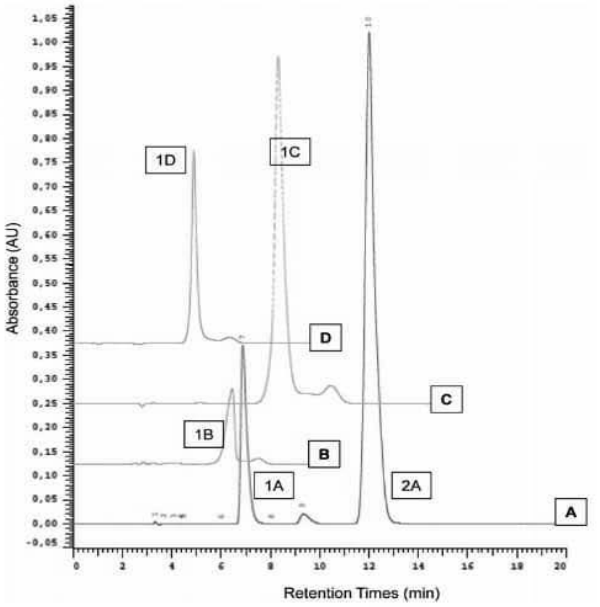

FIGURE 2. Typical chromatograms of four antibiotics chromatographic pics of clavulanic acid (**1A**) and amoxicillin (**2A**) in sample solution coded E1 monitored at 220 nm. Chromatographic pic of ampicillin (**1B**) in a sample solution coded E5 monitored at 254 nm. Chromatographic pic of ciprofloxacin (**1C**) in a sample solution coded E5 monitored at 278 nm. Chromatographic pic of metronidazole (**1D**) in a sample solution coded E5 monitored at 319 nm. This figure appears in color at www.ajtmh.org.

From our results, we can hypothesize that the occurrence of surgical site infections and antimicrobial resistance in the six Beninese hospitals[22] is not a result of poor-quality antibiotics used for prophylaxis.

Our study results are strengthened by the anonymous and in situ samplings. The antibiotics analyzed were selected on the basis of results previous studies that audited antibiotic prophylaxis practices in surgery. The hospitals where sampling was performed were from different levels of the healthcare system. Brand and generic drugs were sampled from various manufacturers, providing diversity to our sample. The samples were analyzed using low-cost and validated methods, with feasibility of routine testing in developing countries such as Benin.

Because of the lack of equipment, we did not perform the endotoxin test on the samples to guarantee their nonpyrogenic status. Because this study comprised only six hospitals located in southern Benin, our results cannot be generalized to the whole country because of unequal means and supply possibilities in hospitals far from the economic capital (Cotonou). Nevertheless, all hospitals can procure medicines from the legal, public, and central provider, Société Béninoise pour l'Approvisionnement en produits de Santé [SoBAPS]; EX-CAME), which has many offices across the country.

CONCLUSION

This study contributes to the evaluation of the quality of the antibiotics used primarily in surgical infection prophylaxis in Benin. To the best of our knowledge, this is the first study to assess the quality of intravenous antibiotics used in surgery. The Beninese national agency of quality control (Agence Nationale de Contrôle de Qualité des Produits de Santé et de l'Eau; www.ancq.bj) performs tests before all drugs are marketed, but during marketing, testing is performed mostly for oral forms. This study included 33 samples of 30 units collected from six hospitals. Results showed that 97% (n = 32) of the samples passed the visual inspection, 100% (N = 33) of the samples passed the pharmacotechnical tests and identification of active ingredients, and 88% (n = 29) passed the dosage of active ingredients; the remaining 12% of samples carried a risk of overdosage, with four of the five samples of

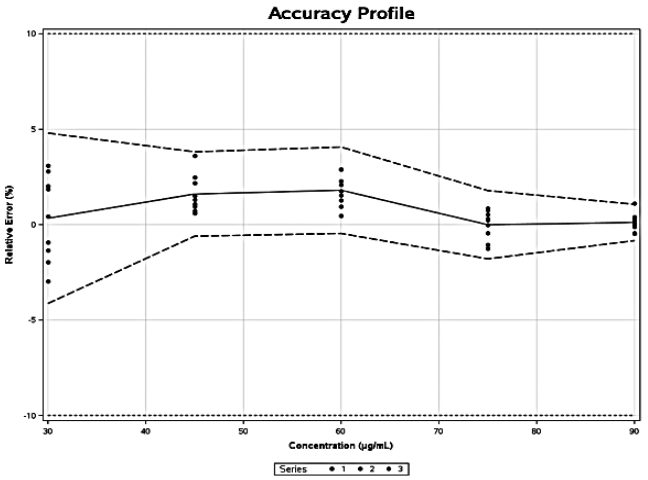

FIGURE 3. Accuracy profile obtained by using linear regression model. The plain red line is the relative bias, the dashed blue lines are the β-expectation tolerance limits, and the dashed black lines represent the acceptance limits. The dots represent the relative error of the back-calculated concentrations and are plotted with respect to their targeted concentration. This figure appears in color at www.ajtmh.org.

gentamicin sulfate not conform to the specifications of USP in terms of dosage. All the samples (100%, $N = 33$) passed the sterility test. Apart from the gentamicin, this preliminary study confirms the good quality of the antibiotics administered for surgical infection prophylaxis in Benin. Our results help reassure prescribers of the reliability of the formal drug supply chain and enable patients to be confident in the drugs provided via the formal supply route. In the context of rare routine laboratory controls, this study showed good feasibility of tests. The quality of antibiotics is a cornerstone in infection prevention and control. Thus, regular, large-scale analyses in various hospitals are important to maintain appropriate healthcare.

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CHAPTER 4: User fee exemption policy formulation impacts antibiotic prophylaxis practices in caesarean section in Benin: a qualitative study.

Submitted to *Health Policy and Planning*
IF 2020/2021: 3.344

Chapter 4 overview

The study in this chapter is a qualitative study performed to understand the disagreement of healthcare professionals with the user fees exemption policy in caesarean section in Benin and their lack of confidence in the antibiotics in the kit. To this end, we interviewed the stakeholders involved in the formulation of the policy.

Background

- User fees exemption is one of the health financing mechanisms used in low- and middle-income countries to protect vulnerable populations from the negative effects of healthcare expenditures.
- Barriers to adherence to healthcare policy recommendations on antibiotics are poor awareness and knowledge of the guidelines, healthcare workers' unclear roles in the management of antibiotics, a lack of standardized processes to ensure proper antibiotics administration, and a lack of end-user involvement in the initial development of the recommendations.

Inputs from this chapter

- A low involvement of concerned stakeholders in policy formulation emerged from interviews.
- Interviewees perceived an hierarchization of healthcare professionals' opinions in decision-making.
- A good appreciation of the setting up of the kit with antibiotics included was reported by the interviewees.
- A low evidence-based and mixed-consensual opinion on the selection of antibiotics for prophylaxis were highlighted.
- The policy formulation was under central command (top-down approach).

Manuscripts submitted to Health Policy and Planning

User Fees Exemption Policy Formulation Impacts Antibiotic Prophylaxis Practices in Caesarean Section in Benin: a Qualitative Study.

Abstract

Many sub-Saharan African countries have introduced or are developing health financing reforms including a user fee exemption policy to facilitate access to various maternal health services including caesarean section. In Benin, the user fee exemption policy for the caesarean section have been introduced in 2009, with a kit containing the required consumables and drugs, including antibiotics to be used for prophylaxis and after caesarean section. Our previous investigations on the use of the antibiotics in the kit showed poor antibiotic prophylaxis practice, a low level of healthcare professionals' knowledge of antibiotic prophylaxis, and some disagreement on the policy. To understand the policy formulation process and how it can impact practice and the selection of antibiotics for prophylaxis in the kit, we carried out a qualitative study using a semi-structured interview guide for stakeholders involved in the formulation. The collected data were analyzed by content analysis. Four main themes emerged. The themes *"Involvement of stakeholders on the policy formulation process"* and "*Perceived top-down approach in the formulation*" revealed poor commitment and less consideration of the stakeholders' opinions, and high control of the government in the formulation. Under the "*Purpose of the setting up of the kit*", the stakeholders expressed positive opinions about the kit that was meant for patient's safety and protection and good practices in the caesarean section, but in the theme "*Criteria and perception of the antibiotics selection"* it was highlighted a low evidence-based and mixed-consensual selection of the antibiotics.

The stakeholders' empowerment and the evidence-based decision in policy formulation can help increase adherence to recommendations to achieve adequate practices and ensure patients 'safety in the caeserean section.

Key messages

- A top-down approach in policy formulation was perceived as high paternalism the Benin government which impacts stakeholders' commitment to poli implementation.
- Low evidence-based decision-making and mixed consensual in the selection antibiotics impact antibiotic prophylaxis practices.
- The empowerment of stakeholders is essential to improve adherence recommendations and ameliorate practices at the local level.

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Introduction

According to the World Health Organization (WHO), health financing is a core function of health systems that can enable progress towards universal health coverage by improving effective service coverage and financial protection (WHO, 2022). The 2005 World Health Assembly called for universal health coverage (UHC) in health systems (WHO, 2005). WHO defined this as securing "access to adequate health care for all at an affordable price"(Carrin and James, 2004). For many countries, achieving UHC require reforms in their health financing systems so that people have financial protection while accessing quality health care (Odoch, Senkubuge and Hongoro, 2021). As part of an effort to achieve the UHC goal of the Sustainable Development Goals (SDGs), many sub-Saharan African have engaged or are engaging in many health financing reforms to facilitate access to services, promote quality, and contribute to regulating healthcare practices. User fee exemption is one of the health financing mechanisms used in low- and middle-income countries to protect vulnerable populations from the negative effects of healthcare expenditures (Agyepong and Nagai, 2011). As in several other sub-Saharan countries, Benin has engaged in some key health financing reforms including a user fees exemption policy (UFEP) for caesarean section. Since 2009, a free kit containing required medicines, including antibiotics and materials, is made available in 48 accredited hospitals at the launch of the policy. The management agency named "*Agence Nationale de la Gestion de la Gratuité de la Césarienne*" (ANGC) heads the management of the policy which covers the free kit and some procedures required for caesarean sections (Dossou *et al.*, 2018). The UFEP improves the affordability of CS, increases their rate (Centre de Recherche en Reproduction Humaine et en Démographie-Bénin, 2014), and reduces poor outcomes for mothers and children including maternal mortality (Ouédraogo, 2013). However, previous studies analyzing the policy reported various misfunctions at different levels of the healthcare system, and patients' opinions on the policy (Lange *et al.*, 2016; Mongbo *et al.*, 2018; Dossou, 2019). No previous studies on this policy reported on how it influenced the use of medicines in the kit, especially antibiotics in the context of the increasing antimicrobial resistance and the call for rational use of antibiotics by the WHO (WHO, 2019).

From the data of our previous study in 2016, we found a poor practice of antibiotic prophylaxis (use of broad-spectrum antibiotics in inappropriate doses and prolonged course of administration) (Dohou, Buda, Yemoa, *et al.*, 2022), and in a mixed-methods study in 2017, we found a low level of healthcare professionals' knowledge of antibiotic prophylaxis and some disagreement with the policy (Dohou, Buda, Anagonou, *et al.*, 2022). The misuse of antibiotics has a major impact on the prevalence of antimicrobial resistance and induces consequences for patient safety (Barbosa and Levy, 2000). In 2019, antimicrobial resistance has been identified as one of the top 10 threats to global health by the World Health Organization (Kakkar *et al.*, 2020). Guidelines for healthcare professionals are key to safe practice (Solà *et al.*, 2014). Several studies showed poor adherence to recommendations on antibiotic use worldwide

(Abdel-Aziz *et al.*, 2013; Putnam *et al.*, 2015; Abdel Jalil *et al.*, 2018). This nonadherence was explained by barriers such as poor awareness and knowledge of the guidelines, healthcare workers' unclear roles concerning the management of antibiotics, a lack of standardized processes to ensure proper antibiotics administration (R. Gonzales, M.A. Handley, S. Ackerman, 2013), and a lack of stakeholders' involvement in the initial development of the recommendations (Jeffrey R. Avansino *et al.*, 2011). In the frame of the UFEP in CS in Benin, little is known about how antibiotic prophylaxis was considered during the formulation and implementation.

As antibiotic prophylaxis is essential in CS, we aimed to understand the process of policy formulation with a focus on the selection of the antibiotics in the kit. To reach our objective, we carried out a qualitative study with stakeholders involved in the formulation and policy management in Benin.

Materials and methods

In January 2020 and March 2021, we performed a qualitative study of stakeholders involved in the UFEP formulation with a focus on the choice of antibiotics in the kit for prophylaxis, using a semi-structured guide (Appendix 1). We used the consolidated criteria for reporting qualitative research for designing and reporting this study (Tong, Sainsbury and Craig, 2007). The purposive sample was based on both direct contact and snowball effect. Two of our interviewees were identified when we were sharing data from our previous studies. They personally proposed to give their point of view on the policy and they later recommended the others. Meetings were conducted face-to-face by the principal researcher of the study (female, external hospital pharmacist, and PhD student), who performed previous quantitative and mixed-methods studies on antibiotic prophylaxis in hospitals (Dohou, Buda, Anagonou, *et al.*, 2022; Dohou, Buda, Yemoa, *et al.*, 2022). All interviewees are medical doctors. Four of the interviewees were met for the first time on the day of the interview. One of them was a senior government official who worked in the mother and child health department. He mainly piloted the formulation of the policy. Another one was a senior government official who worked at the central level of the healthcare system. Two were headmasters at the implementing agency and the two others are practitioners in public and private hospitals. Because of the limited logistical means, we performed interviews with stakeholders living in Cotonou and Abomey Calavi (South of Benin). The questions of the guide were open-ended and explored their opinions on the objective of the kit, the process of the involvement of the stakeholders, and the selection of antibiotics for prophylaxis. The guide did not require any updates during the study. At the beginning of the interviews, we briefly presented the results of the previous studies realized in the hospitals and then explained the objective of the current study. The interviewees were assured that there was no good or correct response or opinion. Providing their own opinions and sharing their personal experiences were the objective of the interview. Data collection was performed anonymously and confidentially. The interviews were recorded with mobile phone dictaphones and verbatim were transcribed. One of the interviewees did not accept

the recording, so field notes were taken. According to their personal experience, some of them did not respond to all the questions of the guide. The discussions took place in their offices (in 4 cases), in a restaurant for one of them, and at home for the latter. Interviews lasted 15 to 35 minutes. We stopped the data collection when we did not have other participants to interview in the area of our study.

We also collected administrative data at the central management agency (ANGC) about some workshops that took place after the formulation in 2014 and 2015 to harmonize practices in CS.

To fit the frame of our interview guide, data were analyzed by content analysis using an inductive process specifically a "manifest analysis" in which we stood on "what the interviewees have said". Two researchers under the supervision of one senior clinical pharmacist, and the promotor of the research proceeded with the analysis of the data. The analysis process comprised five steps based on the process drawn by Bengtsson (Bengtsson, 2016). The steps are described in **Supplement S1, and Supplement S2** described the rigor and assurance of the study. After analysis, feedback was given to the interviewees to have their agreement on the way we analyzed data and then they gave written authorization for publishing.

Ethical approval

This study was approved by the institutional review board of the "Faculté des Sciences de la Santé of Université d'Abomey Calavi" under reference number: 012-19/UAC/FSS/CER-SS.

Results

Six healthcare professionals were interviewed face-to-face in January 2020 and March 2021. The participants' characteristics are summarized in **Table 1**.

Four main themes and fourteen codes emerged from the analysis and can be used to describe the involvement of the stakeholders, the process of the policy formulation, the purpose of the kit, and the selection of the antibiotics in the kit. **Table 2** displays the themes and codes that emerged.

Theme 1: Involvement of stakeholders in the policy formulation process

The UFEP formulation in Benin was a long process with numerous workshops. Several stakeholders from all levels of the healthcare system were involved. Namely, technical stakeholders in mother and child health structures, healthcare policymakers, midwives' association, scientific societies of gynecologists and anesthetists, some pharmacists, hospitals managers, and representatives from public and private hospitals (which were approved to implement the policy), and from all regions of the country.

After we asked questions about the involvement of the microbiologists, interviewees attested that they did not participate in the process of policy formulation. Thus, they were not involved in the selection of antibiotics despite the importance of

local ecology in the efficacy of antibiotic prophylaxis. Another declared that it was because the microbiologists were in limited number at this time in Benin.

Theme 2: Perceived top-down approach in the policy formulation

One of the interviewees thought that the choice of the participants to the UFEP formulation was a diktat, and the policy initiative was highly under central control. This perception of the choice of stakeholders who would be involved in the formulation process as a diktat showed that "the debate" was not open to all the real stakeholders who were concerned. This statement was reinforced by another senior government official who declared that they just took the opinions (mainly about the selection of antibiotics) of some central-level actors to quickly formulate the policy.

Throughout the various workshops, in addition to the absence of some categories of healthcare professionals, those who deserved to contribute to the decision-making seemed to not be associated with the formulation process. Some stakeholders did not appreciate the process of the UFEP. An interviewer related that the authorities could provide the frame of the new practices in CS (in terms of speed, and preparedness of the concerning teams), and invite all hospitals to conform to it. Furthermore, he denounced with insistence the high paternalism of the government in the formulation process. Statements and perceptions of interviewees might suggest a top-down approach in the formulation process.

Theme 3: The purpose of the setting up of the kit

Several reasons were reported to be the purpose of the setting up of the caesarean kit in Benin. Focused on the role of antibiotics, one interviewee argued that the kit was made available for patient protection against infection occurrence, even if the hospital environment is clean, and other hygiene precautions are respected. Other interviewees reported that the kit is a frame to standardize practices and promote the respect of recommendations in the whole country. It was set up to provide standard and quality care for all women who have undergone CS independently of the socio-economic statute or origin. The kit also helps to have required items gathered and then shorten the time to start a caesarean section.

One of the senior government officials who managed the formulation of the policy declared that the kit was set up to deal with “the third delay” in healthcare. As he explained, in Benin, people met three delays before access to healthcare: the delay in taking the decision to go to the hospital, the delay due to the lack of infrastructure (absence of proper means of transport and the bad state of the roads), and the delay linked to the non-availability of materials and medicine to start care on time after diagnostic in hospitals.

Theme 4: Criteria and perception of antibiotics selection

First of all, both pharmacological and non-pharmacological criteria were reported for guiding the selection of antibiotics. The three intravenous antibiotics available in the kit (ampicillin, gentamicin, and metronidazole) should be used in

different regimens according to the level of complication of CS. Among pharmacological criteria, an interviewee stated that the selection of the antibiotics was guided by their effectiveness, their security, and the fact that the antibiotics are common in healthcare professionals' practices. Contrariwise, another declared that the antibiotics available in the kit are not efficient. He argued that based on the antibiotics in the kit, the regimen of utilization that emerges is mixed between prophylaxis and therapy, and does not work as expected. He added that despite their use, the occurrence of hospital-acquired infections was frequent in women undergoing CS.

Non-pharmacological criteria mentioned were in terms of availability and cost of the antibiotics. Often under generic label, the three antibiotics were usually purchased by the hospitals in the public central supplier, SoBAPS (*Société Béninoise pour l'Approvisionnement en produits de Santé*; EX-CAME). This supplier has many branches over the country and is specialized in supplying of hospitals. Based on data available in the report of the harmonization workshop of 2014, the total cost of the antibiotics was US$2.62 for simple CS and US$7.26 for complicated ones.

Secondly, according to the declaration of the manager of the agency, antibiotics were chosen based on all the stakeholders' habits and agreement. Moreover, there is no protocol imposed in terms of dose to administer and duration of administration. Each health professional is free to practice his antibiotic prophylaxis regimen. In contrast, others argued that the selected antibiotics were based on the obstetricians' practices. This statement echoed those declared by the senior government official in terms of the alignment in the previous kit available in hospitals since 2006; before the UFEP formulation. In fact, an actor attested that the selected antibiotics were not conformed with conventional recommendations, and he was not associated with its selection. He also argued that the antibiotics for prophylaxis in CS should be cephalosporins of the second generation. It appears that the selection of antibiotics seemed not to be consensual.

Finally, the interviewees did not report any discussion about the concern of antimicrobial resistance in Benin during the selection of antibiotics.

In sum, the selection of the antibiotics in the kit was based on the usually-used and available medicines and some healthcare professionals' habits with low evidence-based considerations.

Discussion

This study explored the process of the UFEP formulation and the selection of antibiotics for prophylaxis in CS in Benin. It was aimed to understand the bottlenecks of improper practices of antibiotic prophylaxis, and healthcare professionals' disagreement on the policy we reported in our previous studies (Dohou, Buda, Anagonou, *et al.*, 2022; Dohou, Buda, Yemoa, *et al.*, 2022). We then interviewed six stakeholders who were involved in policy formulation and management. Two main determinants emerged from our analysis: the approach adopted in the formulation and the level of evidence in the selection of antibiotics.

1- Top-down approach in policy formulation

The poor involvement of some stakeholders in the formulation revealed by the interviewees appeared as an obstacle to the implementation of the policy in the hospitals. This finding echoed the report of Dossou *et al*. who showed in his Benin study that the low involvement of stakeholders in the formulation had a negative impact on the implementation of the policy at the hospital level (Dossou, 2019). Apart from microbiologists who were not involved in the process, we noted a multidisciplinarity among the stakeholders involved. But some stakeholders felt like their opinions were not considered. In fact, interviewees reported a high control of the government in the choice of the stakeholders invited which was perceived as a diktat. This perception was designated under the word "paternalism" which *is* ***"an attitude and practice that are commonly, though not exclusively, understood as an infringement on the personal freedom and autonomy of a person (or class of persons) with a beneficent or protective intent"*** (Thompson, 2013). With regard to the definition and considering the fact that one senior government official declared that they just took into account the opinions of their colleagues at the central level for some decisions, we hypothesize that the formulation of the policy was conducted following a top-down approach. As defined in *Political pipeline* (21 February 2013), ***"the top-down approach is a clear-cut system of command and control from the government to the project, which concerns the people"***. This approach works on clear and consistent goals drawn at the top; knowledge of pertinent causes and effects; a clear hierarchy of authority; rules established at the top and policy is aligned with the rules and the resources/capacity to carry out the commands from the top (*Top-down and Bottom-up Approaches within Implementation*, 2013). As stated by P. deLeon *et al*, policy in a top-down approach is implemented with standards that the citizens do not understand, which might circumvent their rational preferences (Peter deLeon; Linda deLeon, 2002). In healthcare, the top-down approach puts floors on quality. In this case, care providers become a consumer of the healthcare decision not a stakeholder and/or an implementer

On the contrary, the bottom-up approach begins the implementation of policy with the target groups and service deliverers. Bottom-uppers find that the target groups are the actual implementers of policy (Matland, 1995). In this approach, goals, strategies, and activities must be deployed with special attention to the people the

policy will directly impact. An experience in Suriname (South America) revealed that the bottom-up approach drives change and creates sustainable adherence (Verschueren *et al.*, 2019). This bottom-up approach was described by one of our interviewees who thought that it would be better if the government gives the mains directives of the policy and permits local stakeholders to work for context-tailored guidelines. In this way, all concerned care providers will feel like stakeholders, and that could improve the adherence to recommendations of antibiotic prophylaxis in CS.

2- Evidence in the selection of the antibiotics

The setting up of the kit with required materials especially the antibiotics for prophylaxis in caesarean section shows its importance in the prevention of post-operative poor outcomes (Kandil *et al.*, 2014).

Firstly, our interviewees perceived the purpose of the CS kit containing antibiotics in various ways: to protect patients against the occurrence of infections, to standardize practices in the whole country, and to reduce the timing of caesarean initiation. Globally, we think that the purpose of the kit was perceived as positive and as "good intent". In any case, these statements correlated with the objectives of the policy and echoed the statement reported in a study by Carlès *et al.*: "*the surgical antibiotic prophylaxis kit reduces the emergence of bacterial resistance by assuring the better application of the guidelines and better antibiotic efficacy at the patient level, and by optimizing antibiotic administration and thereby attaining the purpose of the guidelines, which is to lower the risk and number of surgical site infections*" (Carlès et al.,2006).

Secondly, effectiveness was reported as one of the criteria which guided the selection of the three antibiotics in the kit. As known, antibiotics for prophylaxis have to be efficient on the majority of germs (Eholié, Emmanuel Bissagnéné Crémieux and Girard, 2013). Even if the variable effectiveness of the three antibiotics available in the kit (ampicillin, gentamicin, and metronidazole) has been shown years ago (Louie et al., 1982; O'Leary et al., 1986), recent data showed high rates of bacterial resistance to some of the selected antibiotics (A.-T. *et al.*, 2006; Affolabi, 2012; Ahoyo *et al.*, 2014). From current data, the most recommended antibiotic is the cephalosporin of the first generation (cefazoline), either alone or in combination (Mivumbi *et al.*, 2014; Ward and Duff, 2016; Auboyer *et al.*, 2017; WHO, 2021).

The selection of antibiotics for prophylaxis might base on local ecology to avoid antimicrobial resistance influence. Based on our interviewees' declarations the issue of antimicrobial resistance seemed not to be considered during the process. That shows the low level of scientific evidence in the decision-making. Furthermore, the selection made depended mainly on the standard practices of a specific group of healthcare professionals: the gynecologists without the anesthetists' opinions, despite their important role in prophylaxis prescription (Dlamini *et al.*, 2015). As a result, anesthetists did no longer feel like stakeholders; they perceived a hierarchization between stakeholders and divergent consideration of the opinions. As reported by J. Broom *et al.*, hierarchization within and between surgical and anesthetist specialties

influences antibiotic prescribing decisions (Broom *et al.*, 2018). This can be a source of frustration and can explain the non-adherence to the recommendations of antibiotic prophylaxis observed at the hospital level (Dohou, Buda, Anagonou, *et al.*, 2022; Dohou, Buda, Yemoa, *et al.*, 2022). The analysis of the data revealed low evidence-based decisions and mixed consensual opinions on the selection of antibiotics for prophylaxis in CS.

The perceived top-down approach in the formulation with the low involvement of the stakeholders, coupled with the lack of scientific evidence and mixed consensual evidence in the selection of the antibiotics were contrary to the two important principles highlighted in Formoso's methodology of guidelines (Formoso, Liberati and Magrini, 2001). Firstly, a valuable contribution to finalizing healthcare decisions can and should be made through the participation and balanced judgment of specific stakeholders, such as patients, physicians, administrators, and other healthcare professionals. Secondly, in evidence-based healthcare decision-making, scientific evidence should be highly relevant, be gathered systematically, and be appraised critically at the patient and policy levels. In sum, the choice of antibiotics in UFEP in CS was based neither on the consensus between the stakeholders nor on evidence-based data.

Literature reported that the UFEP contributes to the ease of performing the CS and probably within the 30 min which is acceptable between decision and act (Boehm, 2012) and removes stress onto healthcare workers and burden onto families (Lange *et al.*, 2016). In that way, the policy agenda (avoid detention of women and their newborn babies in hospitals because of non-payment of their bills) (Dossou *et al.*, 2018) was reached, but the quality of the care provided remains important. It appears important to improve the healthcare professionals' adherence to guidelines to improve the quality of antibiotic prophylaxis.

In addition, central authorities should take into account the changing bacterial profile and antibiotic susceptibility to update antibiotic prophylaxis recommendations in CS. In fact, through the decades, bacterial susceptibility has changed. For example, in 2012, the rate of bacterial resistance to gentamicin was 45-62.3% in nosocomial infections and the bacterial resistance to ampicillin was 86.4% (Affolabi, 2012; Ahoyo *et al.*, 2014). In 2019, the rate of bacterial resistance to ampicillin increased to 99.2% in surgical site infections (Yehouenou *et al.*, 2020). Therefore, the evidence-based data on antimicrobial resistance currently available supports the antibiotics updating and should be taken into account with at least as much attention as cost and availability.

The participants interviewed were those who lived in Cotonou and Abomey Calavi. We are aware that participants from other regions of the country can have different opinions according to their experiences. The first strength of our study is the solidity of our data which was expressed as "information power" by Malterud *et al.*. The concept of "information power" suggests "*that the more information the sample holds, relevant for the actual study, the lower amount of participants is needed*"(Malterud, Siersma

and Guassora, 2016). In our study, the participants were from various qualifications and different backgrounds and were personally involved in the formulation, implementation, and management of the policy. The second strength is that the study was designed and conducted by pharmacists based on the results of previous studies and helped to understand the process of the UFEP formulation, and the selection the antibiotics. The third is that in the data analysis, we collaborated with an external analyst who brought her point of view on the data which provided an additional value. Overall, our study provided a complementary understanding of available literature insofar as it addressed the aspects of the process of the UFEP formulation, and the selection of the antibiotics and helped to explain the dysfunctions observed in local implementation. To our knowledge, our findings were the first of a kind and can help to improve the process of selection of medicines in health decision-making and provide avenues of research in other settings like Benin.

Conclusion

The formulation of the UFEP in Benin was conducted under the control and command of the government and was managed by the national agency working. The main findings in this study were the top-down approach in policy formulation with poor involvement of the stakeholders, the hierarchization of the stakeholders' opinions, the low-evidence-based criteria, and the non-consensual decision-making in the selection of antibiotics available in the kit. From all these findings, it results in that the formulation did not follow a strong methodology to ensure the sustainability and good implementation of the policy. The stakeholders' empowerment and collaborative approach will help to address disagreement, and then to rise adherence to policy recommendations for good antibiotic prophylaxis practices and safe care for women in the caesarean section.

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Table 1: Characteristics of participants

Variable	Characteristics	Value
Number of participants		6
Sex n (%)		
Female		4 (66.7)
Male		2 (33.3)
Qualification	Anesthetist	1
	Gynecologist	1
	Medical doctor with other specialization	4
Occupation	Workers in hospitals	2
	Current/Former headmaster of ANGC	2
	Former senior government official	2
Professional statute	Professional active stakeholders	4
	Retired stakeholders	2
Involvement level	Policy formulation	1
	Policy management	3
	Policy implementation (Practitioners)	2

Table 2: Summary of themes and codes that emerged from the analysis

N°	Themes	Description of the themes	Codes and illustrative quotes
1	**Involvement of stakeholders in the policy formulation**	Informs on the stakeholders involved in the UFEP formulation and their provenance.	- **The representatives were from the whole country: the technocrats, and healthcare system stakeholders** *"We did so many workshops. There were Regional Health Directors, hospital managers, other resource people, and people from the ministries"*. (Interviewee 1) - **The practicians of the hospitals were involved** *"We had several meetings and there were some workshops but I do remember that the Benin Gynecology and Obstetrics Society was involved in the discussions. The Order of Midwives was represented too. There were a few pharmacists and some anesthetists"*.(Interviewee 2)
2	**Perceived top-down approach in the policy formulation**	Describes the perception of the stakeholders on the formulation process	- **The choice of the stakeholders was a diktat** *"Yes, but those professionals were selected by the ministry… it was a diktat. Personally, my view was that this initiative was too paternalistic"*. (Interviewee 2) - **The setting up was in a top-down approach** *"So it was only fair that the government should say that from now on if you do a caesarean we will pay you. But what we want is that when you decide to do a caesarean, within 15 minutes the woman is on the table and you are operating. What we do not want to happen is that after you make the decision, only then do you start looking for the medicines and staff to do the caesarean"*. (Interviewee 2) *"No, for the first time, we discussed with some of our colleagues at our central level in policy formulation. After that, we submitted the choice to stakeholders for validation. We had to work quickly…"* (Interviewee 6) - **High paternalism in the setting up** *"Personally, I did not like the fact that there was this system in place. It would have been better to encourage people operating in the hospitals to get together and standardize things, rather than doing everything for them. If you want, you could say that it shouldn't be each hospital with its own fee schedule but that there should be standardization between hospitals. As it is, you are issuing directives and it is up to them as technicians to have discussions themselves and come up with their own standard"*
3	**The purpose of the setting up of the kit**	Inquiries about the reasons for making available the CS kit.	- **The kit for patient protection** *"When your operating theatre is completely clean and sterile, and your instruments are sterile, you cannot say 100% that there are no germs. There still could be 5% in the air and others in specific places... so you have to do something to protect the patient"*. (Interviewee 1) - **The kit for uniform practices and respecting recommendations** *"The kit was introduced so that everyone is using the same thing right across the country. So it is like a protocol, right? The main aim is to make sure everyone uses the kit in the same way. Appropriate use means only using the items they tell us to."* (Interviewee 1) - **The kit to reduce the timing of CS initiation** *"It is better to have the medicines ready so that when you decide to do a caesarean, you can just take them out and use them. It also prevents situations where there is a shortage of specific products. That's why we put together a kit. This is where the idea came from to create a kit with all the medicines and consumables needed for a caesarean"* (Interviewee 2) *" The intent of the kit was to have medicines and required materials gathered to avoid the 3rd delay in healthcare access"* (Interviewee 6)
4	**Criteria and perception of antibiotics selection**	Reveals the criteria followed in choosing the antibiotics and stakeholders' perceptions	- **The pharmacologic criteria: antibiotics are efficient** *"Because we knew that Ampicillin, Gentamicin, and Metronidazole (in some cases we do have to use Metronidazole as well) would solve the problems"* (Interviewee 1) - **The non-pharmacologic criteria** *"The antibiotics were chosen on the basis of availability, accessibility, and cost"*

			(Interviewee 3) - **The antibiotics are not efficient** *"Yes, in practice it is a mixed protocol, somewhere between antibiotic prophylaxis and short-course antibiotic therapy. If people felt completely secure with us, they would not stay beyond 48 hours. But they are not sure everything is going to be OK. That definitely leads to quite a few hospital-acquired infections"*. (Interviewee 5) - **The choice of the antibiotics was based on usual practices and was not imposed** *"The choice of antibiotics in the kit is based on standard practice among those involved. This is a protocol that has been agreed between practitioners. The kit was not imposed by the agency"*. (Interviewee 4) *" The antibiotics in the kit are which have been used since 2006 in the emergency kit available in the hospitals. Healthcare workers used to use them…"*(Interviewee 6) - **Antibiotics chosen were not conformed to conventional recommendations** *"If we were to follow the rules of antibiotic prophylaxis, the same products that are already being used for curative antibiotic therapy should not be offered as first-line treatment. They have not really followed the advice on antibiotic prophylaxis. If we had to agree on something, it would be second-generation cephalosporins... I was not involved when they chose that"* (Interviewee 5) - **Antimicrobial resistance was not a concern** *" No, I never heard anyone talking about antimicrobial resistance. It was not discussed"*(Interviewee 1)

Supplement S1: Steps of data analysis

Steps	Activities	How it was conducted
Decontextualization 1	Identification of meaning units	Separate coding was performed by the 2 junior analysts using the verbatims of 2 face-to-face interviews.
Contextualization	Checking the aspects of the content has been covered regarding the aim of the study	Polling of the codings and live discussion between the 2 junior analysts.
Categorization	Creation of coding tree (codes and categories) and validation with the 3rd senior analyst	Group the meaning units (codes) into categories and draw the coding tree and validation.
Decontextualization 2	Analysis of the remaining interviews based on the coding tree	Coding by the junior analysts using the coding tree.
Compilation	Creation of the themes and final debriefing by the three analysts.	Creation was performed by the 2 junior analysts by linking the codes and categories into themes. Final debriefing by the 3 analysts

Supplement S2: Rigor and quality assurance

Reflexivity	• The study is a part of a project which aims to implement a multidisciplinary strategy for prevention and infection control in hospitals. It had a background and focused on a specific aspect of the purpose (use of antibiotics in the context of UFEP), and was designed by pharmacists to understand previous results of non-adherence to the recommendations of antibiotic prophylaxis at the hospital level. • The main investigator (DAM) has a background in hospital pharmacy and performed an observational study in the operating room and a mixed-methods study on healthcare workers in obstetrics. She was trained and had experience in qualitative research methods. • The main investigator and co-authors were not included in the setting up or the management of the policy to limit the risk of response bias.
Credibility	• Participants in the study were involved in the UFEP formulation, implementation, and management. Data collection was done by the main investigator who designed the study. • Data analysis was performed by 3 pharmacists from different countries including the main investigator. Two were aware of the context of the study framework; one was a foreign, junior analyst bringing an external point of view on the subject. • Data analysis was in five steps (separate codings; pooling, and discussions by the two junior analysts; creation of the coding tree, and its validation with the 3rd senior analyst; final coding of the remaining interviews; and creation of the themes + final debriefing) • Findings checked with those reported in the literature (especially studies in Benin).
Transferability	• The qualification and occupation of the participants were variable. • The participants were stakeholders in the policy formulation, implementation, and management and two of them worked in different kinds of hospitals (private and state-owned hospitals).

Appendix 1: Semi-structured interview guide

Research question

What is the perception of the actors involved in the setting up process of the free caesarean-section policy on the choice of the antibiotics in the kit in Benin?

Investigator introduction

I'm DOHOU Angèle, a hospital pharmacist and PhD student in clinical pharmacy. I'm performing research on the use of antibiotics in obstetrics, especially in Caesarean-sections. After my research in some Benin hospitals on the use of the antibiotics in the kit, I would like to know how the antibiotics were chosen and what is the perception of the actors involved in the kit setting up.

The interview will last 30-45 minutes and will be recorded. I would like to have your agreement for the recording. I will give you a transcription of the interview back. I assure you that the data collected will be analyzed anonymously. All information you can give and your personal experience are welcome and can help to understand the subject.

Interviewer introduction

Mr./Mrs.... What are your profession and occupation? What was your role in the process of policy formulation and the kit setting up?

1- How was the committee of the kit setting up constituted?
2- How were you chosen among the committee members?
3- What were the health system actors involved in the formulation process? Were there some microbiologists?
4- In your opinion, what was the purpose of the caesarean sections kit in the context of the free policy?
5- What were the criteria for the selection of antibiotics for prophylaxis?
6- For which kind of usage, the antibiotics in the kit were available? (Prophylaxis or therapy).
7- Who was involved in the selection of antibiotics?
8- Was antimicrobial resistance concern discussed before the selection of the antibiotics?
9- What is your personal opinion on the kit (especially the antibiotics)?

CHAPTER 5 : Patients' perception of Infection Prevention and Control in surgery in Benin: a qualitative study.

In preparation

To be submitted to American journal of infection control IF 2022: 2.908

Chapter 5 overview

The study in this chapter is a qualitative study performed with patients to explore their knowledge of healthcare associated infections and antibiotic utilization. Two socio-anthropologists interviewed 30 patients in two different hospitals. The findings of this study can help to appreciate to what extent patients in the Benin setting can be involved in Infection Prevention and Control.

Background

- Infection Prevention and Control includes patient participation since patient engagement in care is shown to improve health outcomes.
- In high-income countries, the desire for collaborative action between patients and healthcare professionals is often reported.
- In low-income countries, a high level of self-medication with antibiotics is spread, data for collaboration between patients and healthcare professionals to raise awareness of antibiotic use are scarce, and the level of knowledge of HAI and antibiotics is little known.

Inputs from this chapter

- Patients in the Benin setting patients have some awareness of hospital-acquired infections and the means of their transmission.

- Patients' perceptions of antibiotics were erroneous and sometimes did not have any link with infectious diseases.
- Communication around patient care provided by healthcare workers in surgery was poor.

Patients' Perception of Infection Prevention and Control in Surgical Settings in Benin: a Qualitative Study.

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ABSTRACT

Background: In the context of antimicrobial resistance, Infection Prevention and Control, and rational use of antibiotics are strong recommendations for all stakeholders including patients. Patients engaged in care improve healthcare outcomes. In low-income countries, patients' perception of Infection Prevention and Control is little reported.

Aim and methods: To explore the perception of healthcare-associated infections and antibiotic utilization, we interviewed patients who had undergone surgery. Two socio-anthropologists collected data over two months in 2019 in two hospitals' digestive and obstetric wards. Data were analyzed by 3 pharmacists using inductive content analysis.

Result: Thirty patients were interviewed. From data, it emerged that patients have some awareness of hospital-acquired infections and the means of their transmission. Concerning antibiotic utilization, their perceptions were erroneous and sometimes did not have any link with infectious diseases. Healthcare workers' communication with patients about healthcare-associated infections and the purpose of antibiotics was poor.

Conclusion: Patients' perception of IPC revealed some current potential that deserves room for improvement. This potential can be improved by implementing tailored activities of patients' education in IPC based on the context including a clear dialogue between healthcare workers and patients around healthcare-associated infections and the purpose of antibiotics.

Keywords: Patient perception, healthcare-associated infections, antibiotic utilization, communication, surgical setting, Benin.

1 BACKGROUND

Surgical patients are at risk of infections, especially surgical site infections, with numerous impacts on health, quality of life, and also a burden on public health [1]. To prevent and cure these infections, surgical teams refer to antimicrobial utilization. Unfortunately, antimicrobial use was reported to be inappropriate with consequences of increasing antimicrobial resistance (AMR), a global threat [2]. To improve the situation, the World Health Organization (WHO) recommended the reduction of the incidence of infectious diseases, increasing knowledge and awareness about AMR, and promoting the rational use of antimicrobials [3]. To achieve this recommendation, the Infection Prevention and Control program is key.

Infection Prevention and Control (IPC) is a practical, evidence-based approach that prevents patients and healthcare workers from being harmed by avoidable infections, and, as a result, decreases the risk of antimicrobial resistance [4]. IPC contributes to achieving the 3rd (promote good health and well-being) and 6th (provide clean water and sanitation) sustainable development goals [5] and occupies a unique position in the field of patient safety, high-quality health service deliveries, and universal health coverage [4]. However, although healthcare workers have a great responsibility for quality and safe care, patient engagement has to be taken into account since there is increased literature that describes the desire for collaboration between healthcare workers and patients in healthcare decision-making [6], [7].

Vahdat et al. define patient engagement as "*the involvement of the patient in decision-making or expressing opinions about different treatment methods, which includes sharing information, feelings, and signs and accepting health team instructions*" [8]. Also referred as "patient-centered care" or "patient involvement", patient engagement showed an improvement in healthcare providing [9]. Several studies on hand hygiene reported the benefit of patient involvement in their hand hygiene [10]–[14]. Patient engagement requires the patient to have knowledge and skills, supported by education and training but also the recognition of this partner as important by healthcare workers [15], [16].

Although patient participation in healthcare is a trend, several countries do not integrate it into their healthcare system. Some guidelines recommend providing information on IPC measures as a means of patient involvement in the IPC program [17]. Two kinds of information are necessary for the patient: (1) information on Standard Precautions that intent to prevent contamination such as hand hygiene, respiratory hygiene/cough etiquette, vaccination (mostly against influenza), etc., which may be incorporated into the patient information materials provided on admission; (2) and Transmission-Based Precautions (TBP) that intent to avoid dissemination which are printed in fact sheets, pamphlets or other materials including information such as the rationale for the additional precautions, risks to household members, room dedication for TBP, directions for use of Personal Protection Equipment by family members and visitors. Transmission-Based Precautions

information is essential in the home environment where families often have primary responsibility for adherence to infection control recommendations [18].

In low-income countries, data about patient engagement in care are scarce [19] although the risk of postoperative complications is higher which needs improved surveillance [20]. According to Ji Y.P et al., in low-income countries, recognition of the family as caregivers or inclusion of them in the IPC strategies is not included in the guidelines [17]. In these later settings, in the absence of provision of antibiotics by the hospitals, patients must purchase themselves the antibiotics required in surgical care (pre-, intra-, and post-operative). Then, they endorse the responsibility of healthcare workers, but they are not qualified like them. As a result, there is an important solicitation in terms of expenses for healthcare (because no insurance coverage is available), and the ability to follow instructions about the care given. Patients' engagement in healthcare and adherence to the therapeutic project appears then important.

In Benin, the IPC program is not yet available in hospitals, and data about patients engagement in healthcare are not available. However, after discharge, the management of surgical wounds and antibiotics utilization are done by patients or their families. Considering the delicacy of the care following surgery, we interviewed some patients who underwent surgical interventions to explore their perception of healthcare-associated infections and antibiotic utilization in Benin. This exploration could help appreciate their abilities to participate in IPC interventions and antibiotic management to promote their safe care in surgery.

2 METHODS

The study method was developed in collaboration with a team of socio-anthropologists from the University of Abomey Calavi.

The research team and reflexivity

Data collection was carried out by two female researchers from the University of Abomey Calavi working with health workers on population welfare issues. They were in the process of seeking information to document health care conditions and enable their improvement. One had a professional master's degree in project management and local development and had been an individual consultant for a previous project. The other had a master's degree in socio-anthropology of health and is a junior consultant for projects. They were both research assistants in charge of collecting and managing qualitative data. They had no prior relationship with the interviewees, no particular research motive, or personal goals. They were service providers for the project. One bias that could be related to them is that they were not used to the surgical setting.

Ethical approval

The study was approved by the Institutional Review Board of the Health Faculty (FSS, Benin) under reference number: 012-19/UAC/FSS/CER-SS.

All the patients included in the study (or parents of children) provided oral consent.

Study design

The data collection consisted of individual semi-structured interviews in convenience sampling. Appointments were made face-to-face. Content analysis was used for the data analysis. Some people (patients' families, and other patients) were around where the interviews took place, but they did not participate in the discussion.

Over three months, the research assistants conducted open-ended interviews with patients of digestive and obstetric surgeries (caesarean section) wards of two hospitals: "Hôpital Bethesda" (private confessional and peripheral level) located in Cotonou, and "Centre Hospitalier et Universitaire de Zone Abomey-Calavi / Sô-Ava (CHUZ AB/SA)" (teaching zonal and peripheral level) situated in Abomey Calavi

Then, they identified 30 surgical patients (15 per hospital) to conduct in-depth semi-structured interviews with each of them about their perceptions of antibiotic prescribing/utilization and healthcare-associated infections. Data collection was carried out at the patients' homes or in the hospitals. The questions, primers, and prompts were prepared by the researchers, the interview guide was not pre-tested. The interviews had not been rehearsed. The interviews were conducted in the local language (Fongbé) for the majority and recorded by audiotape. A field notebook was used. The duration of the interviews varied from 22 minutes to 2 hours and 7 minutes. The saturation point was not discussed and the sample size was defined in advance. The socio-anthropologists listened to the interviews and translated them into French during transcription. The transcripts were not returned to the participants for comment or correction.

Analysis and findings

The descriptive data associated with the interviewees and the interviews were grouped using Excel software. The qualitative data processing was done manually with the word. After transcription in word software, data were analyzed using inductive content analysis methods—specifically, a "manifest analysis," in which we stood on "what the interviews have been said" without straying from our research questions. The data analysis was performed by three pharmacists. In the beginning, a team of two pharmacists, PhD students trained for the qualitative analysis proceed to the coding of the transcriptions. The first step was about a separate coding of 2 interviews selected at random (1 from each hospital) by each analyzer. The second step was a meeting for debriefing and discussion between the 2 analyzers. At this step, we defined the meaning of consensual codes that emerged. In the third step, another

couple of interviews were selected as previously and were coded separately but 1 by each analyzer based on the preliminary tree. After the pooling of both coding trees, a novel tree was built and a discussion took place with a senior clinical pharmacist, the promoter of the study. It resulted in a final coding tree which was used in the last step by both PhD students to code the remaining interviews together. This option was done because the interviews were long and there had a wide variety between interviews since patient experiences were different. It allowed us to make the discussion instantaneously. At the end of coding, the codes were grouped in themes and the report was done. The themes were about the perception of healthcare-associated infections by patients, their perception of antibiotics, the use of antibiotics before and after hospital admission, and communication around care.

3 RESULTS

3.1 DESCRIPTION OF PARTICIPANTS

Thirty-three patients were contacted to be interviewed. Three people refused to participate in the study for reasons not reported. The characteristics of the patients are summarized in table 1 below.

Table 1: Participants' demographic and clinical characteristics

	Age (years)	Gender n (%)	Type of surgery n (%)
Participant characteristics	30.1±1.9 Min: 11 Max: 57	M: 06 (20) F: 24 (80)	Digestive: 11 (36.7) Obstetric: 17 (56.7) Mixed: 01 (03.3) Other: 01 (03.3)

3.2 INTERVIEWS FINDINGS

Three main themes and eight codes emerged from data analyzed to inform patients' perceptions of healthcare-associated infections and antibiotics utilization.

3.2.1 knowledge of healthcare-associated infections mechanisms

3.2.1.1 Patients' knowledge of healthcare-associated infections

The knowledge of healthcare-associated infections (HAI) by patients was variable. Some of them declared that they can contrate an infection in the hospital, others do not have any idea of HAI. Those who had had an infection after their surgical intervention did not link with the intervention. Others did not know the symptoms of HAI.

> *"Good! I didn't know it, but I just got that knowledge."* (Patient16, 31 years old, Male- Visceral)

3.2.1.2 *Vectors of healthcare-associated infections*

Numerous vectors were pointed out by patients in the transmission of infections. Perceived as hospital-acquired infections (that included according to the WHO, nosocomial infections and HAI), patients stated that hospital is one of the vectors of HAI. They supported their opinions by the fact that patients in hospitals share rooms, beds, and bathrooms.

> *"I can't name a disease, but there are various kinds of diseases in the hospital and you can get infected with them."* (Patient04, 37 years old, Female-Caesarean)

Some patients declared that an infected patient can also be a vector of disease. Several ways of transmission were described like hand touch, respiratory droplets, and aerosols through cough or sneeze, spit on the ground inducing contamination when walking barefoot. They also pointed out that the fact of sharing utensils like plate, cup, and wrap to cover the bed can be a vector of infection. Cholera, tuberculosis, and fever (refer to as Lassa fever) were particularly named by some of them.

> *"The infections especially the fevers we are talking about now, the viruses because of the mode of transmission, you just have to touch the person or all the time we are together, we used to cross each other, we are face-to-face; the other can cough there and it can come to you"* (Patient09, 29 years old, Female-Caesarean).

Others argued that a patient who does not pay attention to his or her hygiene in the hospital and does not take care of the meal or bed can contract an infection.

> *"Because there are several diseases in the hospital, you have to make the effort to take care of yourself; otherwise you can contract another disease in the hospital and go home with it."* (Patient18, 47 years old, Female-Visceral)

Finally, health providers were also pointed to be a vector of infection. The surrounding of the patients can also infect them as reported by this patient.

> *"If the health workers also don't take care of them, they can make you infected and you will go back with it. That's why they forbid us to touch things. And that they care a lot"* (Patient18, 47 years old, Female-Visceral).

Although the patients did not have a precise idea of HAI (infection contracted during care providing), their statements showed that they have some understanding of Infection Prevention and Control.

3.2.1.3 *Means of prevention against healthcare-associated infections*

When we asked the interviewees about the means of prevention against HAI, some of them focused on non-pharmacologic precautions to protect the surgical wound against infections. Others focused on how to take care of themselves in the hospital. To protect the surgical wound, patients used the means at hand to avoid water getting into it as described in the quote below.

"For my toilet, I take a sachet with which I hide the wound with tape and I wash. Well, as they said that water should not touch the wound." (Patient16, 35 years old, Male-Visceral)

None of them referred to pharmacologic prevention such as antibiotics used before intervention (antibiotic prophylaxis), hand hygiene, and sterilization of surgical instruments. Nevertheless, one of them argued that they have to follow medical prescriptions and caregivers' exigences for avoiding infections.

"In order not to contract a disease, one must..., first, one must first follow the prescriptions, that is to say, the requirements of doctors and nurses, especially the doctor." (Patient01, 31 years old, Male-Visceral)

Personal hygiene in the hospital was declared to be an essential way of prevention. Patients often argued that avoiding touching their surrounding things, do not walk barefoot, and sit down everywhere can protect against infection. Also, eating diet-balanced food, taking care of bed and meals, practice hand hygiene after the toilet was described to be a way of prevention.

"When you go to the hospital it's not everything there that you have to touch, or go to the hospital and sit on the floor, not find a place to sit, everyone must know how to behave in the hospital." (Patient18, 25 years old, Female-Caesarean).

3.2.2 Patients' perception of antibiotics utilization

Concerning the antibiotics' utilization by patients undergoing surgery questions were asked about the sources, they used to know about this class of medication, their perception of antibiotics' indications, and their habits of utilization.

3.2.2.1 Sources of information on antibiotics

Some of the patients, know about antibiotics from the previous prescription they received at the hospital.

"It's when we go to the hospital and the doctor prescribes this drug for this disease, it is how we know the drugs." (Patient24, 35 years old, Female-visceral)

Other argued that they know about medicines from informal vendors in markets, in informal shops, or at the edge of streets.

"When you go to the drug sellers and explain your problem to them, they advise you to take such and such a drug." (Patient30, 28 years old, Female-Caesarean)

Friends' and relatives ' advice was also reported to be a source of information on antibiotic utilization.

"Yes, it was someone who advised me, he also suffered from stomach aches and he says that it often calms that" (Patient08, 36 years old, Male-Visceral)

3.2.2.2 *Auto medication with antibiotics*

The utilization of antibiotics without healthcare workers' prescriptions was spread among the interviewees. Some of them used antibiotics from informal sources when they were sick.

> *"My stomach hurt so much that I had to take a medicine I had once paid for at the market that apparently should relieve stomach aches".* (Patient16, 35 years old, Male-Visceral)

When a patient takes antibiotics without medical instructions, the use is not appropriate. A wrong dose of antibiotics and a short duration of administration were practiced. But patients stated that they felt better, and satisfied after utilization.

> *"No I take two. When I start by feeling the pain I take two. When the pain stops I stop. Yes, when I take it, I feel a satisfaction in my belly."* (Patient18, 47 years old, Female-Visceral)

From the analysis of the statements of the patients, those who underwent digestive surgery started their therapeutic course by auto-medication including antibiotics. Others started with medication based on medical plants.

> *"It remained like that until the father made him a product "amassin"* (which means medical plant medicine in local language) *from Nigeria which he brought and he drank the product".* (Patient02-mother of a baby, 18 years, Female-visceral)

All the patients interviewed on the link between the irrational use of antibiotics and the occurrence of antimicrobial resistance did not have any knowledge about it. Some of them declared that antibiotics are superior to other medicines.

3.2.2.3 *Perception of the indications of antibiotics*

Patients revealed numerous indications about antibiotics. The patient's level of education of the patient can influence the indication they gave to antibiotics. Sometimes, they make confusion between prevention and therapy. For example, a license graduated stated that antibiotics are to cure infections but the description she gave about her situation described the preventive role of antibiotics.

> *"No we did not find any infections, since I have a cesarean section, to be infected will be fast because I am more exposed; there I see that when we operate you are more exposed that's why we administer antibiotics."* (Patient09, 29 years old, Female-Caesarean)

The majority of the patients independently of their level of education attested that antibiotics are used for avoiding the suppuration of wounds, cicatrizing, or healing of wounds. Others argued that antibiotics « fortify » them after surgery.

> *« What I do know is that antibiotics heal wounds»* (Patient05, 29 years old, Female-Caesarean).

The interviewees often compared all antibiotics to the "amoxicillin" or described the antibiotic using the words "long tablet".

> *"There are some that are a bit longer and look like amoxicillin. It's for the wound."* (Patient15, 33 years, Female-Caesarean)

A great proportion of our interviewees indicated that antibiotics cure all kinds of diseases. Whether it can be a pain, stomachache, rashes, abscesses, cough, fever, or malaria (in combination with antimalaria medicine).

> *"Amoxicillin is the pain einh when I have pain in the body, for example, I take it to calm the pain a little."* (Patient03, 25 years, Female-Cesarean and Visceral)

For others, antibiotics were used in absence of no disease. Some affirmed they take it from time to time just to feel well. One of the interviewees declared that he used to take antibiotics because of the dust.

> *"I take amoxi because of chalk, I am a teacher, taking my machine to go to work, you see the dust I am going through."* (Patient20, 42 years old, Male-visceral)

The perception of antibiotics expressed by the patients is a fear of infections and a desire to prevent or cure them. It also revealed the attention patient paid to their health even if the means used deserve room for improvement.

3.2.3 Communication around patients 'care

3.2.3.1 Communication on care provided depended on patients

Concerning their recent surgical intervention, some patients, mostly women, declared that they were not informed that they would undergo a caesarean section after unsuccessful vaginal labor. Some of them had an explanation when they asked about what was happening.

> *"After that, they didn't tell me anything anymore. They examined me a second time and they said they were going to shave me. That's when I retorted by saying that they didn't tell me I was going to have an operation, and they shave me? That's when they told me that it was after analyzing my condition that they said that. After that, they didn't tell me much anymore."* (Patient24, 35 years old, Female-Visceral)

On contrary, the patients in visceral surgery were informed that they were going to have an intervention even if the information was incomplete.

> *"No, as he said appendicitis there, in the room he said nothing more"* (Patient08, 36 years old, Male-Visceral)

Having no competence in the health domain, women who underwent caesarean section expressed the need to have explanations from healthcare workers about the

state of their health. That can help them to prepare themselves psychologically or to ask other questions to better manage their health for good healing.

> *"I think for antenatal consultations, they have to manage to explain things better to us. Because it is the one who examines us who knows what we are suffering from. Because we don't know anything about health."* (Patient26, 29 years, Female-Caesarean)

Even after the interventions, most patients stated that healthcare workers were more focused on the care they had to give. Information on post-operative care and precautions against hospital-acquired or healthcare-associated infections were not given.

> *"They didn't tell us anything. When they come, they only do the injection and they leave."* (Patient02-mother of a baby, 18 years, Female-visceral)

However, one of the patients declared that she received advice from healthcare providers after her intervention. Advice reported by the patient was related to the prevention of surgical site infection.

> *"The healthcare workers had advised me to manage myself so that the threads did not break, not to let the water enter the dressing at the risk of rotting the wound, not to defile the wound by putting dirty clothes on the body, so I follow this advice."* (Patient15, 33, Female-Caesarean)

For discharge, all the patients received a prescription of *per os* antibiotics. Some of them reported that they received an explanation of the antibiotics' indication and posology.

> *"Yes; otherwise, after prescribing the drugs, he came, he explained to me a little bit the role that it plays."* (Patient16, 31 years, Male-visceral)

Others argued that they were aware of the posology orally from healthcare workers or sometimes healthcare workers just pointed out the posology on the boxes.

> *"They don't explain it to us like that, but they point it out to us, as it's done here. For example, these drugs about which you asked me questions, they did not explain their role to me, they only gave me the dosage, but they told me that it was because of my suppurative wound that they prescribed these drugs."* (Patient29, 32 years old, Female-Caesarean)

In certain cases, patients did not pay attention to what the healthcare workers said. Some of them follow instructions given to other patients.

> *"The midwife was telling the one next to me to put away her amoxicillin tablets and I put away mine also."* (Patient27, 25 years, Female-Caesarean)

Other patients, even if they did not have medication information, they did not ask to understand.

« I don't know, I didn't ask ».(Patient13, 17 years old, Female-Visceral)

Even if, several patients attested to follow the directives they received on the medications, one of the patients declared to reduce the dose of antibiotics she had to take because of adverse effects expressed in terms of *"it shakes me up"*.

> *"Because when they tell me to take two tablets and I take them, it shakes me up. That's why I lower the dose."* (Patient26, 29 years old, Female-Caesarean)

3.2.3.2 Lack of communication about wound infection

Contrary to other patients, certain look for explanations to understand the evolution of the state of their health. A patient infected described the occurrence of surgical site infections in other patients in his hospitalization room.

> *"No, not at all; but when I put the problem to the doctor, he told me that it was because it was already gangrenous; but I found that for the other also were suppurated. There is a little boy who was in front there that they operated on the 5th of this month and for him also suppurated. I do not know if it is..."* (Patient19, 36 years old, Male-Visceral)

4 DISCUSSION

This qualitative study aimed to explore the surgical patients' perception of healthcare-associated infections and antibiotics utilization. We discussed below the three main themes that emerged from the data collected.

Firstly, from our participants' statements, we noticed they were aware of the existence of infections that can be contracted in hospitals and knew various means of transmission. Although IPC was not implemented in Benin hospitals and considering the fact that this study was performed before the COVID-19 pandemic, our patients' perception revealed a good potential of knowledge of IPC that can be improved. Most of them pointed out hygiene concerns, hospital sanitary, patients' and healthcare workers' behaviors which can be a source of contamination. These components cited are perfectly included in IPC and have to contribute to safe healthcare [4]. The hospital was identified as a vector of infections because of the state and the lack of adequate infrastructure. That was the same report made in Ghana settings where several interviewees declared that hospitals were unclean and were identified as a site where the administration of care may be associated with infections [21]. Indeed, a previous study performed in one of the hospitals included in our study showed that there were various germs on the surfaces of the hospital, and suggested that can be a risk of healthcare-associated infections [22]. In a Burkina Faso study to assess HAI risk in a first-level hospital, all three components studied (hospital population, healthcare, and services organization including hospital environment) were reported to represent a high-risk source of infection [23]. We think that the awareness campaigns during the

COVID-19 period might reinforce people's awareness and improve hygiene level in hospitals.

In this study, some of the patients indicated using personal means to protect the surgical wound dressings. That appeared challenging firstly in a hospital environment where infrastructures are scarce and because patients are not skilled for the care given. Sanger P. et al. reported some challenges that impact patients' ability to manage post-discharge surgical wound complications such as required knowledge for wound monitoring from discharge teaching, self-efficacy for wound monitoring at home, and accessible communication with their healthcare providers about wound concerns [24].

A part of personal hygiene that patients underlined, hand hygiene sensitization has to be a core concern for patients and their families to avoid microorganisms' dissemination and/or contamination of surgical wounds and prevent hospital-acquired infections to parents and visitors. This is important since a study showed that patients' hands also can be a source of contamination [25]. Moreover, patients' involvement in hand hygiene showed improved outcomes in care [12], [16], [26].

To improve the potential that patients expressed in our study, we think that it is important to raise the awareness of HAI and provide adequate knowledge tools to patients for IPC including causes and consequences of HAI, means of prevention namely the importance of antibiotic prophylaxis, and hand hygiene, wound monitoring at home and adherence to treatment including antibiotic prescription. These tools tailored according to the Benin context can be grouped under Standard Precautions and Transmission-Based Precautions information that Siegel et al. recommended providing to patients [18].

Secondly, we found that the knowledge about antibiotics was derived from previous medical prescriptions, relatives' recommendations, or the informal system. These findings echoed findings from previous studies performed in Benin, Cameroon, and Pakistan [27]–[29]. However, in our study, participants did not mention general practitioners, pharmacists, or information from media and social media, as sources of information, as reported by Teke et al. [27]. Patients revealed several indications for antibiotics which did not have any link with bacterial infections. Their reports were closer to the correct indication when their education level was high. This confirms the link between education and the rational use of medicines highlighted by the WHO [30].

Self-medication was a recurring practice for some of the interviewees either in their previous habits or for the current pathology that brought them to the hospital. Since the therapeutic course in our setting begins with self-medication, it appears urgent to improve health literacy and awareness among Benin people to avoid misuse of medicines and decrease the rate of complicated diseases before people decided to go to the hospital. This becomes essential specifically concerning antibiotics because of the high rate of AMR in Benin and the low variability of antimicrobials available to face infectious diseases [31].

Thirdly, from the interviewees' declarations, it appeared that communication between patients and healthcare workers was poor. Although healthcare workers provided patients with information about the antibiotics prescribed for discharge, some desired to know about the care they are going to receive (before intervention), and others were looking for explanations about the evolution of their disease. This can lead to hypothesizing that healthcare workers make a certain segmentation in the healthcare as if a part belongs to the providers (clinical care) and the other part concerns the patient (discharge care). In our opinion healthcare have to be in global concept. According to Vahdat S et al. appropriate information about the diagnosis and treatment is important for providing safe and quality services [8]. The lack of communication on antimicrobials was reported to drive patients to other sources of information with varying degrees of quality (internet, information leaflets, and local pharmacies) [6]. In our study, the sources patients had indicated to use seem to be of the least quality (mostly relatives). A qualitative study in the United Kingdom in 14 patients who received antimicrobials in the 12 previous months reported a failure in information provision and communication with infection management [6]. That failure influenced patients' future ideas about infections and their management and alters their future actions toward antimicrobials driving poor prescription adherence and loss of follow-up [6]. These findings reinforced the importance of patient engagement in the rational use of antibiotics.

In the same trend, Muehlhauser I. et al. reported that *"Non-compliance in patients is rarely provoked by intention or laziness. Thus, patients should not be the first to be blamed for the lack of therapeutic efficacy"* [32]. The lack of providing necessary information and skills to patients was reported to be an essential cause of insufficient treatment outcomes. In a study performed in Switzerland in 2013, although communication between the different actors in the hospital was recognized to be important, healthcare workers had considered and seen it as a waste of time because of the burden of hospitals' activities and frequent emergencies [33]. Otherwise, based on the report the interviewees gave about information provided by healthcare workers around the surgical intervention, we noticed that there is a difference according to the type of surgery (visceral versus caesarean section). For visceral surgery, since patients have to pay for all required materials, laboratory analysis, and medicines before the intervention initiation, they were informed. On contrary for caesarean sections which has a free kit for intervention, some patients declared to not been informed before. In the latter case, the intervention initiation does not depend on the patients' ability to pay. Nevertheless, this difference in information provided can also be because caesarean sections are often emergency cases. In all cases, it would be fair to inform patients equally.

Another fact, we would like to highlight is the case of one patient who chose to reduce the dose of the antibiotics by herself because of certain side effects. This can be due to the lack of communication with the healthcare workers. Probably, she did not

such as the bias of translation because the interviews were done in the local language and then translated into French. Also, the interviews were done by socio-anthropologists but data analysis was done by pharmacists who did not attend the interviews.

The strengths of this study are the appreciative number of patients we interviewed and the variety of hospital and surgical disciplines we included. The fact that interviews were conducted by socio-anthropologists added value to the data collection because they are more aware of social sciences and more at ease to discuss with patients about this less studied subject in our setting. Furthermore, this in-depth study provided key knowledge to literature and practices, but also novel themes for future studies such as evaluation of IPC and AMS implementation in Benin hospitals. In addition, the assessment of patients' health literacy will also be interesting to better appreciate their perception and their engagement in care.

From the findings of this study, we can provide some avenues for practitioners to engage patients in care and encourage research in other settings far from Cotonou and Abomey Calavi to compare data and think for a global concept of patient engagement in care in Benin.

5 Conclusion

The place of the patient (or family) in care is uncontestable since his understanding of the disease and the treatment, and the knowledge of medicine (indication, posology, side effects, particular precautions, health public concerns as antimicrobial resistance in the case of the antibiotics, etc.) are essential for the cure and the follow-up. From our study, patients have some awareness of IPC which deserve room for improvement. In our setting where resources are scarce, education and empowerment of patients and family can help them to recognize their needs in health and to access healthcare on time. Healthcare workers have to be trained to recognize the importance of the patients' engagement and how to communicate with them about care.

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General discussion

General discussion

This work helped to gather data on antibiotic utilization in caesarean section and the different determinants that can contribute to the rational use of antibiotics.

1. Key findings of this work

From the five studies performed in our thesis, several findings emerged. Firstly, we found on the one hand a poor quality of antibiotics' usage (oral or injectable) in terms of misuse (inadequate choice of the molecule), overuse (administration for a long time, administration when not necessary), and underuse of antibiotics (administration of underdose). This underdosing resulted from the fact that patients did not buy the complete number of antibiotic prescribed. That can lead to personal and global consequences (post-operative infections and AMR). To avoid this situation, the needed antibiotic have to be available in the hospital kit and should be correctly used by healthcare professionals. On the other hand, the aptitude of the people involved in this utilization deserves room for improvement: patients with mixed knowledge and healthcare professionals often with basic vocational education which does not enable a proper utilization of antibiotics. Overall, practices in each hospital are similar but differed between hospitals according to the type of hospital (national teaching versus zonal), and the qualification of the medical team especially anaesthetist (medical doctor anaesthetist versus nurse anaesthetist). Secondly, we have

highlighted a low level of knowledge of the five conventional criteria of antibiotic prophylaxis among healthcare professionals, and the lack of confidence in the antibiotics available for the caesarean section. Various determinants (i.e. related to the patient's health, healthcare professionals, hospital and central levels organization, and patient behavior) were reported to lead to improper practices of antibiotic prophylaxis. These determinants emerged from the perception of healthcare professionals of the practices of antibiotic prophylaxis. Figure 2 in the published article [106] shows the link between these determinants, and patient is appeared to have a major impact on healthcare professional with consequence of improper practices of antibiotic prophylaxis. It results in that in addition to the others determinants, patient and healthcare professionals should be especially considered in the process of improvement of practices.

From the third study, which assessed the injectable antibiotics' availability and chemical quality, it appeared that the needed antibiotics for prophylaxis were often out-of-stock. A non-neglect proportion of 15% were not conform to the specifications. One of the non-conformity is the dosage of gentamicin in the samples. Considering the side effects of this molecule, paying specific attention in the case of therapy with this molecule since prophylaxis is about a short course. However, the methods used in our study for the dosage of gentamicin can be reconsidered.

The fourth step of the thesis reported the context of the user fees exemption policy formulation in the caesarean section and the selection of the antibiotics in the kit. The findings displayed the absence of a participatory approach in the formulation and the lack of evidence-based practices in the selection of antibiotics in the kit.

In the last step, interviews with the patients show on the one hand that they have a potential of knowledge of infections, and antibiotic utilization deserve room of improvement. In the second hand, healthcare professionals communicated insufficiently with the patients to provide them with information about healthcare-associated infections and antibiotic utilization. Table 4 summarizes the findings from our different studies regarding each stakeholder in the healthcare system. From the data of this table, interventions can be set up and implemented for each stakeholder.

Table 4: Findings emerged from our thesis **(1/2).**

Stakeholders	Findings
Patients	High rate (56.7%) of self-medication with antibiotics Awareness of the risk to be infected, fear of the bacteria and infections Low level of knowledge of healthcare-associated infections Erroneous perception of antibiotics and their indication
Healthcare professionals	Poor practice (69.6% not conform) of antibiotic prophylaxis and overuse of antibiotics Low level of knowledge of antibiotic prophylaxis (15.2%) Lack of confidence in antibiotics (quality and efficacy) selected for CS Desire to be trained to rise their level of knowledge Acknowledgment that the practices must be improved Low adherence to clinical practices guidelines for CS Expression of the need for an active dedicated structure for Infection Prevention and Control Absence of consensus and collaborative work (communication issues) Absence of communication with patients about antibiotic use

Table 4: Findings emerged from our thesis **(2/2).**

Stakeholders	Findings
Hospitals	Unavailability or inappropriate infrastructures or antibiotics Poor performance of supply chain Good quality of antibiotics available in hospital pharmacies Absence or inactivity of dedicated structure for Infection Prevention and Control Poor management of policy at the local level (communication issues)
Policymakers	Meeting the Sustainable Development Goals N.3 (Improve mothers' and newborns' health) Objective to make affordable maternal healthcare services Good intent to make available the kit with antibiotics (patient protection) Low participatory approach in policy formulation Poor evidence-based consideration (AMR and antibiotics selection) Poor methodology in clinical guidelines development (low involvement of stakeholders) Poor management of the policy at the central level (communication issues)

In addition to our data, the other theses in the frame of MUST-PIC project provided complementary data on the topic of Infection Prevention and Control through several studies:

- a study on hand hygiene practice in obstetric and visceral surgeries showed a low level of compliance (33.3% of opportunities achieved) among healthcare professionals, and a lack of permanent hand hygiene infrastructures such as sink, soap, towels and clean water in the hospitals [107], (see abstract in appendix 2),
- an audit on antibiotic prophylaxis in visceral surgery showed a compliance to the five conventional criteria between 0.0-1.5% according to the guideline used (WHO, SFAR, ASHP), and the spread use of broad-spectrum antibiotics [108], (see abstract in appendix 3),
- in the study of the bacteriological profile of microorganisms responsible for surgical site infections, 85.2% of germs had positive aerobic bacterial growth, and most of them were multidrug resistant [109],
- the unpublished data study on the structure that manages hospital hygiene and nosocomial infection named "Comité de Lutte contre les Infections Nosocomiales" (CLIN) showed rare organization of their activities and low availability of healthcare workers to conduct the activities.

The analysis of these variables data shows a need for global intervention to improve Infection prevention and control in Benin hospitals.

2. Critical appraisal

2.1. Research relevance

The goal of this thesis is to provide on the one hand scientific knowledge in the field of antibiotics utilization in caesarean section and to propose concrete ways and tools for improved clinical practices on the other hand. To reach our research aim, we used several methods to conduct the studies.

i) Observational study

For this three-level study, we used patient medication history, prospective and observational methods, and medical files to collect data. Patient medication history is a record of the past treatment of a patient with the intention to have relevant information and detect any problem of inappropriate use of medicine [110]. The patient medication history helps to have an idea of the patient's habits at home. Asakrh *et al.* analyzed the completeness and comprehensive information of patients' medication data using various sources such as medical files, pharmacy databases, and patient interviews [111]. This represents a challenge in Benin. Because there is no medical recording for outpatient treatment, especially self-medication, it is not possible to have crossed-information from other databases like private pharmacies since the pharmacists in Benin do not hold a database of patients who buy medicines in their pharmacies. In addition, because of the absence of regulation in Benin before February 2020,

people could buy medicines including antibiotics without medical prescriptions, and any kind of medicines in informal stores. In our study, we performed medication history by interviewing patients face-to-face to gather information about their utilization of antibiotics. Considering that the collection was performed in absence of any paper support, for example, a care booklet (commonly used in our setting), the patients could provide imprecise information, and the post-operative context could influence the accuracy of their response due to the psychological impact of caesarean section. However, given that we collected the information from the concerned patient, and considering that the medication history is frequently used to collect information on patient medication at home, we can consider that this method corresponds to the type of collection we did. In addition, patient medical history has a positive evaluation in Truitt *et al.'s* study [112] and was scored to be more performant than other sources in Asakrh *et al.*'s study [111].

In Benin, the most recent data on the use of antibiotics in outpatient dates from 2008 and concerns only medical practice. Our study provides some updated data, on the rate of self-medication with antibiotics and draws attention to the fact that antibiotic utilization in outpatient was spread. It is also a way to raise awareness among healthcare professionals to check what patients use before admission.

The prospective and observational method used to collect data on antibiotic prophylaxis implies selecting the kind of patient we planned to include, watching healthcare professionals in practice, and recording in live data we were looking for. This method permits direct record in a natural environment with the possibility of longitudinal analysis since our presence did not disturb the operators because we did not ask them questions. This method is positive for the operating theater and avoids missing data which can be met in the retrospective study when the records are not correct. Nevertheless, in the observational study, there is a lack of control over external variables that can affect the data collected. Moreover, some biases can be considered such as the Hawthorne effect which describes the change in the behavior of an individual when he or she is aware of being observed. But this effect fades when the observation lasts over time [113]. In our study, the observations lasted one month and we did not notice a change in the practices in terms of the choice of antibiotic for example even if the dose and duration of administration varied from one patient to another one. In addition, the error of human observation, and the recording data could be other biases.

To our knowledge, this study is the first performed in Benin to assess antibiotic prophylaxis practice in caesarean section. In addition to other studies published in the field, our study brought data on antibiotic prophylaxis and the use of antibiotics in the kit of caesarean section in the context of the user fees exemption policy. These findings may be a baseline for performing similar audits in

other surgical disciplines, providing data on antibiotic consumption in surgery. The analysis of the factors that condition good antibiotic prophylaxis such as the socioeconomic status and/or the level of education of the patient, their relationship with the healthcare professional, the type of the hospitals (teaching vs zonal, State-own vs private), the level of knowledge of the healthcare professional, is an interesting study that could be conducted.

As far as possible it can be, the idea of carrying out a retrospective study on the period of our prospective study could be interesting to compare the data and remove the ambiguity of the errors of human observation and the recording data.

In the last step, we collected data on post-natal antibiotic utilization by recording medical files. This method allowed us to have information on patient medication even if the observer was not present when the physician was prescribing. Although this method is about saving time, the record in the medical file can be different from what patients have if there is a change due to any reason and the medical team forgets to update the file. As much as possible, we could perform cross-collection data by checking the patients' medicine or interviewing the patients. But, since the post-natal antibiotic prescription is made for discharge, we cannot meet patients to check these data. It could be considered in future research to plan a post-discharge follow-up phone call to collect this information when patients' phone numbers and consent are available.

The analysis of the utilization of antibiotics at the three levels gives a global view of the situation with a need for improvement at each of the levels. That shows the wide inappropriate use of antibiotics which could explain the high rate of AMR found by *Yehouenou et al.* in Benin [17].

ii) Mixed methods study

In the second study, we collected data using a convergent parallel design study which consists of a concurrent collection of qualitative and quantitative data in the same setting and at the same time on the same topic. The mixed-methods help to analyze the two components independently and interpret results together. It was a kind of concurrent triangulation design in a single phase [105]. The quantitative data scored the level of knowledge of antibiotic prophylaxis based on the five conventional criteria and the qualitative criteria explore the beliefs of antibiotic prophylaxis practice. These objective and subjective complementary data permit us to understand the poor achievement of antibiotic prophylaxis in our previous study. Quantitative scores from many participants provide strengths to weaknesses of qualitative data from a few people. Alternatively, qualitative collection from a few people offers strength to quantitative data that do not provide detailed information about the topic [114].

As defined in the "*Encyclopedia of Survey Research Methods*", a self-administered questionnaire is a questionnaire used to collect quantitative data which was completed by a participant without the

intervention of the investigator [115]. In our study, we used it to collect data on the knowledge of antibiotic prophylaxis with healthcare professionals. The questionnaire was built based on those used in a similar study in Burkina Faso [116], the five criteria of antibiotic prophylaxis, and the aim of our thesis (identify the bottlenecks of rational use of antibiotics). Although the questions were as clear as possible, it could be possible that certain respondents did not understand some of them. This can explain the fact that some respondents did not respond to some questions.

The interview allowed an in-depth exploration of the subject which results in relevant findings, induces less bias, and provides more personal information about the respondent. We also performed focus groups which provided diversity and enrichment of interviewees and responses. Discussions in the group help to have confirmation or not on a specific aspect in situ. Even if it is difficult to organize and sometimes lowers the time of speaking, focus groups permit group dynamics and save time. contrariwise, it provides more limited findings and little personal information about the respondents [117]. As participation in this study was voluntary, it is possible that we did not include participants who had different opinions or specific information about the topic. In addition, during our collection, we did not have interviews with as many gynecologists as anaesthetists. Nevertheless, the triangulation and the multicentric collection of our data strengthen our results.

Our study provided data on the level of knowledge of healthcare professionals and their beliefs in antibiotic prophylaxis. This is the first study on this kind of data in the caesarean section in Benin and that filled the gap of lack or non-updated data in infection and prevention control in general. From this data, improvements in practices can be implemented in the hospitals by considering the determinants reported in our study such as healthcare professionals' level of knowledge, and dedicated structure for infection prevention and control in the hospitals. Further investigations are necessary for exploring the hospital managers to understand their beliefs about the lack of infrastructure and medicines, poor management, and issues of communication. In addition to data provided by Mongbo et al. on the patient's satisfaction with the policy [103], an investigation into patients about the prescription of antibiotics in the context of free policy since it appeared that patient is the major determinant for the proper antibiotic prophylaxis [106].

iii) Qualitative studies

Concerning the interviews with policymakers, the findings permit the understanding of the process of policy formulation and the choice of antibiotics, and the bottlenecks that can impact antibiotic prophylaxis. That can help the health authorities to take a step back from the way they conducted the formulation and choose to make things differently. Our data are complementary to those reported by other studies in Benin. In fact, in the context of the user

fees exemption policy, those studies reported the improved financial accessibility to CS and health services, described mixed efficacy of the policy implementation, related decrease rates of maternal and infant mortalities, pointed existence of additional costs, and reported the patients' good satisfaction with the policy [83], [98], [103], [104], [118].

From interviews with patients, the data provided permits us to know about patients' knowledge of HAI and antibiotic utilization. From this data, it appears urgent to tailor education programs to improve patients' knowledge, and aware that healthcare professionals to recognize the importance of the patient in the care. For more comprehension of patient engagement in care, an in-depth study on their health literacy and healthcare professionals' beliefs on the involvement of patients in care can be interesting. Thanks to a good level of health literacy, as defines by the Center of Diseases prevention and control, people will have the ability to obtain, communicate, process and understand basic health information and services.

All the qualitative data collected in this thesis were analyzed using content analysis. Qualitative content analysis is a descriptive research method consisting of the development of a coding frame and qualitative coding of data. In this method, the data coding follows the frame defined in advance in the interview guide [119]. We used it because of the specific setting of Benin and because our data are the first kind collected in Benin. This gives a wide

expression of the data to allow the emergence of themes and categories particular to our setting. This method permits to read between the lines, to have a deeper knowledge, and fits better small volumes of data like ours. However, the analysis of our data with a framework approach can be considered to compare the results. Also, it will be useful to work in developing specific qualitative analyzing frameworks for the African specific context.

iv) Chemical quality analysis methods

In the framework of this thesis, we also performed a chemical analysis of injectable antibiotics. The majority of the methods used are those from different pharmacopeias (European and US) or validated methods from literature. In addition, we developed and validated a generic and less expensive method to analyze one of the antibiotics (gentamicin). Apart from the fact that this study permitted to control the quality of injectable antibiotics (for the first time in Benin), it also allowed thanks to the MUST-PIC project the equipment of the "Laboratoire de Chimie Analytique et d'Analyse des Médicaments (LCAM) of the "Faculté des Sciences de la Santé" of the University of Abomey Calavi with the possibility to continue performing this kind of analysis.

By way of conclusion, our thesis provided a variety of data to reach the general aim of the project MUST-PIC: "to reduce the healthcare associated-infections by improvement of hand hygiene and rational use of antibiotics". Our findings mixed with those of the other theses of the MUST-PIC project can contribute to set up

the rational use of antibiotics. We also contributed to some of the studies in the two other theses of the project on an audit of hand hygiene in surgery which reported a 33.3% of compliance in healthcare professionals, and an audit of antibiotic prophylaxis in visceral surgery (another common surgery performed in several facilities) which showed the poor practice of antibiotic prophylaxis. The abstracts of the papers are displayed in appendices 1 and 2. Specific data from both theses were: Antimicrobial resistance in hospitalized surgical patients, two biomolecular studies in *Acinetobacter baumannii* and *Escherichia coli*, the audit of nosocomial infection control's committee operation and internal policy on hospital hygiene and use of antibiotics, the assessment of the alcohol-based products and implementation of its production in hospitals, and a qualitative study to understand hand hygiene behavior in a hospital using Theoretical Domain Frameworks. The MUST-PIC project already had positive spin-offs in clinical practice: training on hand hygiene, antibiotic prophylaxis, supply chain performance, and the preparation of alcohol-based products in hospitals with scaling up during the COVID-19 pandemic.

2.2. Strengths

For most of the topics we studied, data were scarce, then our research provided unprecedented lighting in the field, and globally showed the gap that the pharmacist can contribute to Infection Prevention and Control. The other strengths of our thesis are numerous:

- all of our studies were prospective and helped to correct direct data in the hospitals,
- the studied hospitals are from the three levels of the Benin healthcare service that allowed to have a representative and data from various settings,
- studies were carried out successively and in a limited period of time, which makes it possible to make a link between the data
- the majority of the studies was performed basing on a background from the previous data. The studies were performed to answer a specific question about the use of antibiotics in caesarean section.
- the data collections were performed by training teams or often by the principal investigator (the Ph.D. student),
- the studies cover multiples facets of the topic and stakeholders (patients, healthcare professionals, policymakers),
- the data analysis involved external and more experienced analyzers to have a relevant and external appraisal,
- the promotion of multidisciplinary work throughout the studies.

2.3. Limitations

Our studies suffer from some limitations including:

- the restraint localization of the hospitals where we collected our data (the south of Benin). However, multicenter studies

are rare in Benin and we collected data from the three different types of hospitals in the Benin healthcare system. That helped to have an overview of each setting. Thus, we then have some representatives of the hospitals. These studies were pilots and can permit to perform others in others hospitals of Benin because the hospitals in the whole country do not have the same challenge, the same qualified medical teams (teaching hospital has more qualified medical teams than first level hospital); the same level of experience or understanding of problems relating to antibiotic use. Cultural, socio-economic aspects can also influence the use and behavior with antibiotics. In addition means provided by health ministry of Benin in each kind of hospital can different.

- the small size of the samples in our studies, the absence of saturation in the qualitative studies because of financial resources, and the difficulties to include participants,
- the use of the same type of analysis methods (qualitative content analysis) for all of our qualitative data. We opted for this method because of the specific setting where we collected our data: user fees exemption policy, patients have to provide medicine for healthcare initiation. Moreover, quantitative content analysis enables the wide expression of data that fits our setting where this collection was made for the first time. However using the existing frameworks to analyze our data is to be considered and can probably provide another reading angle.

3. Clinical perspectives and intervention to promote rational use of antibiotics

3.1 Recommendations from our findings

From the results of our thesis, many recommendations can be made to the different healthcare professionals and policymakers in IPC specifically for rational use of antibiotics such as raising people awareness about IPC, training of healthcare professionals and providing evidence-based data. Considering the importance of maternal and child health worldwide, particular attention has to be paid to our findings in order to set up and implement interventions for improved healthcare. Detailed recommendations are summarized in Table 5 below.

Table 5: Recommendations to healthcare professionals and policymakers **(1/2)**

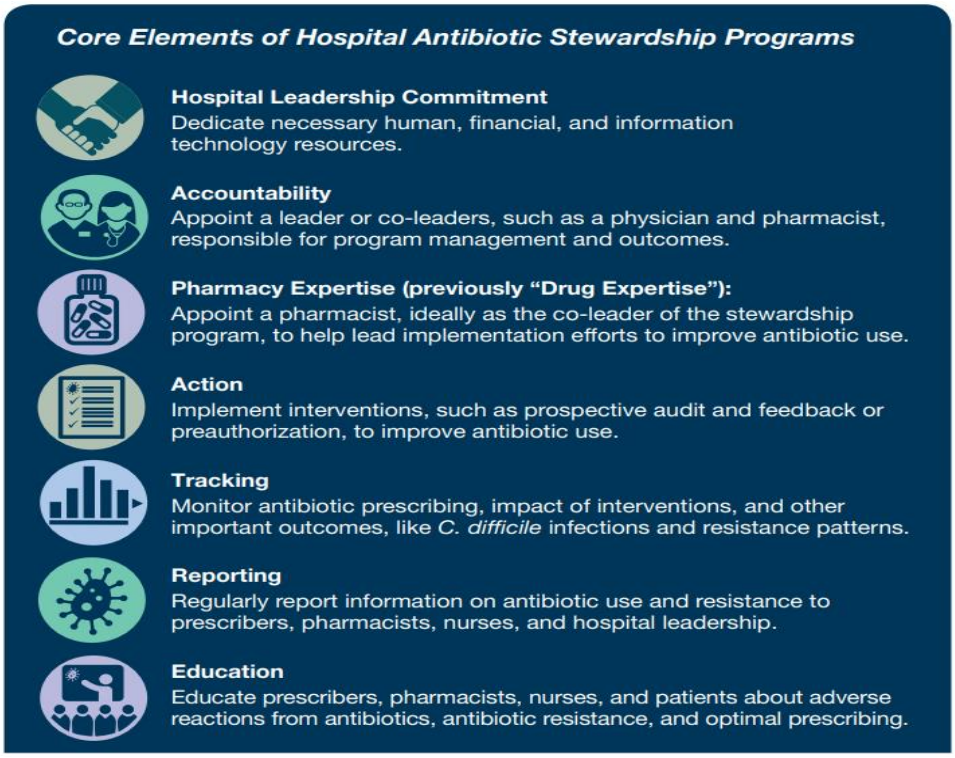
Stakeholders	Recommendations
General practitioners	- Adopt good practices of antibiotic prescription - Provide patient education on antibiotics and AMR - Raise people's awareness about infection and prevention control
Healthcare professionals in hospitals	- Adopt good practices of antibiotic prescription - Improve adherence to clinical practice guidelines - Plan personal training in IPC - Improve communication with the patients around the care - Raise people's awareness about infection and prevention control
Pharmacists	- Improve antibiotics availability in hospital pharmacies and private pharmacies - Promote rational dispensation/use of antibiotics - Raise people's awareness about infection and prevention control - Implement collaborative work with hospitals (public-private partnership) - Involve in research to provide alternatives or new drugs for IPC - Play a cornerstone role in antibiotic use based on new health authorities' recommendations (ABRP) - Ensure the quality of antibiotics, and provide good quality service in antibiotic dispensation (advice, patient therapeutic education)

Table 5: Recommendations to healthcare professionals and policymakers **(2/2)**

Stakeholders	Recommendations
Policymakers	- Set up a national policy action plan - Provide financial and humans resources in the hospitals - Produce and promote evidence-based data and practices by funding research - Implement and boost IPC programs. - Train and aware themselves in IPC disciplines - Develop drug quality analysis labs, market essential antibiotics for antibiotic prophylaxis, - support other initiatives such as MUST-PIC guidelines

The implementation of certain of the above recommendations could be in the frame of the structured program named "antimicrobial stewardship" (AMS) which is a key in Infection Prevention and Control. AMS is defined as a coordinated set of actions aimed at promoting the prudent use of antimicrobials, with the ultimate goal of optimizing clinical outcomes while minimizing unfavorable consequences including resistance selection as well as adverse drug reactions [120]. Figure 4 shows the antimicrobial stewardship program's core components in hospitals. These components include hospital leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, and education [121]. It results in that antimicrobials stewardship programs in hospitals need significant financial resources, trained

human resources, competencies, political commitment, a committed team of experts, and the support of the laboratories that can provide microbiology data and information systems from the hospital [122].



CDC, Core Elements of Hospital Antibiotic Stewardship Programs. 2019.

Figure 4. Core elements of antimicrobial stewardship

Although, there are some initiatives around the African continent [123]–[127], this program is little implemented in low-

income settings and appears to be a challenge in the next years. Frequent surgical disciplines such as obstetric, visceral, and traumatology can be the pilot implementation areas. To succeed in the implementation of the AMS program, some factors have to be addressed such as the issue of a dedicated person to motivate other colleagues (a champion), lack of coordination between hospitals departments, low policymakers' support of facilities, time constraints, competition among doctors, and absence routine antibiograms performing (low availability of laboratories) [128]. In Benin, AMS is not implemented in any hospital. Considering the benefit of AMS implementation in other African countries such as the reduction of antibiotics consumption in terms of defined daily dose per 100 patients in 47 South African hospitals [127], the optimization of the antibiotic prophylaxis criteria in 5 tertiary hospitals in Egypt [129]. Perspectives in research could include the evaluation of its implementation and the financial burden it can induce.

One of the cornerstones of the IPC is the patient, who in low-income countries has a low level of health literacy and is exposed to unsafe care. Considering the magnitude of harm that unsafe care can cause in African settings, and the high rate of HAIs [130], the WHO presented a technical report with solutions for 12 patient safety action areas in all 46 countries in Africa. This report named "African Partnerships for Patient Safety" (APPS) allows partnerships between African hospitals to build strong patient

safety partnerships, focus on tangible patient safety improvements in each partnership hospital, and facilitate the spread of the safety efforts [131]. The 12 patient safety action areas are displayed in Table 6 below.

Table 6: Our thesis contributions (+MUST-PIC) to patient safety action areas (WHO, APPS) **(1/2).**

N°	APPS Patient safety action areas	This thesis' contribution	MUST PIC's contribution in addition to our thesis
1	Develop and implement national policy for patient safety	Provided data for the development of the antibiotic guide for prevention and control of surgical site of infections	Provided antibiotic guide for prevention and control of surgical site of infections (Theses 1, 2, 3)
2	Improve knowledge and learning in patient safety	Revealed the lack of knowledge	Performed study in patient involvement in Hand Hygiene (Thesis 3)
3	Raise awareness among patients and healthcare workers	Revealed the need of patient awareness	Lifted a corner of the veil on the questions during data collections (Theses 1, 2, 3)
4	Adress the context in which health services and systems are developed	NA	Performed qualitative observation in operating rooms wards (Theses 1 and 2*).
5	Minimize healthcare-associated infection	Provided data	Performed Training (Theses 1, 2*, 3*)

Table 6: Our thesis contributions (+MUST-PIC) to patient safety action areas (WHO, APPS) **(2/2)**

N°	APPS Patient safety action areas	This thesis' contribution	MUST PIC's contribution in addition to our thesis
6	Protect health care workers		Provided data on Hand Hygiene (Thesis 3*) Distribution of Alcohol-based products and training for their production (Thesis 2)
7	Protect healthcare waste management	NA	NA
8	Ensure safe surgical care		Hand hygiene - Antibiotic guide (Thesis 3)* - Antimicrobial sensitivity (Thesis 3)
9	Ensure appropriate use, quality, and safety of medecine	Performed the chemical quality control of antibiotics	
10	Promote partnerships between patients, family members, health professionals, and policymakers	Revealed the need for communication in antibiotics utilization and prevention of HAI	Revealed the need for patient involvement in hand hygiene (Thesis 3)
11	Provide adequate funding	NA	
12	Strengthen surveillance and capacity for research	NA	

***= Co author**

3.2 Clinical guidelines developement

Although, data from our qualitative studies with healthcare professionals and actor involved in the formulation showed some disagreement with the user fees exemption policy in CS and antibiotics in the kit, it is important to highlight that in the process of the formulation, some workshops were performed with certain stakeholders of the healthcare system. That shows the willingness to involve the end-implementers in the formulation, but there is a non-adherence to the antibiotics in the kit in local level. In addition, the choice of antibiotics was described to be done at the central level and based on the previous kit available in the hospitals since 2006. The kit could be considered as a guideline for the clinical practice of caesarean section. Considering these previous statements, the development of the kit has to follow as possible as the process described by the WHO in its handbook and which we presented in chapter 2, Table 2. Based on some findings we mentioned in Table 4, we underlined two points that have to be considered in the kit updating: the multidisciplinary work in local level and the evidence-based decision-making. Table 7 shows our findings and the WHO's process useful steps for efficient kit setting up that could improve adherence.

Table 7: Our thesis findings and WHO's process important steps

Findings in policymakers	WHO
• Low participatory approach in policy formulation. Poor methodology in clinical guidelines development (low involvement of stakeholders) • Poor evidence-based practice consideration (AMR and antibiotics selection)	• Convene a multidisciplinary panel to oversee the development of the guidelines • Review the scientific evidence • Formulate the guidelines

To raise adherence to guidelines of antibiotic prophylaxis, their development has to involve a multidisciplinary team with specific competencies in the domain which could conduct the development with expertise. In the case of guideline development in CS, this team has to include gynecologists, anaesthetists, midwives, microbiologists, pharmacists, epidemiologists, etc. This team defines the composition of the guideline and includes the opinions of the representative stakeholders. In this case, a bottom-up approach is relevant for effective results. This bottom-up approach was used in the framework of the MUST-PIC project through the Delphi method.

The evidence-based decision-making is a process used to determine the best intervention for a population, it is shaped based

on community needs, practitioner experience, and existing evidence [132].

In addition to the practitioner experience, the choice of antibiotics for prophylaxis in CS has then to be done based on the existing evidence to reinforce the guideline's relevance. The Benin CS kit contains three antibiotics (ampicillin, metronidazole, and gentamicin). Based on the results from studies on antimicrobial resistance in 2015 and those of the MUST-PIC project in 2020, 94% and 91% of the germs isolated in the surgical infected sites were resistant to ampicillin, one of the antibiotics in the kit [17], [133]. In 2007, a study in Ghana assessed the efficacy of these three antibiotics (ampicillin, metronidazole, and gentamicin) vs amoxicillin + clavulanic acid and concluded that the three antibiotics were less efficacy than amoxicillin + clavulanic acid [134]Other studies also showed that ampicillin presents less efficacy for prophylaxis in CS [135], [136]. In view of this evidence, the antibiotics in the Benin CS kit have to be updated to ensure the safety of the women undergoing CS.

In the framework of the MUST-PIC project, based on the various results we gathered and through a Delphi method with a panel of national and international experts, we set up a guide for the rational use of antibiotics for the prevention and control of surgical site infections (see appendix 4). The Delphi method is a systematic process of forecasting by collecting the opinions of panel members through several rounds of questions [137]. These

members are experts, and knowledgeable about a specific topic, and their opinions throughout the rounds allow them to reach a consensus about a subject. The Delphi method we used embedded the observations we made in the study on the user fees exemption policy by following a bottom-up approach and evidence-based data. In the antibiotic guide setup, we made based on antibiotics available, recommendations for antibiotic prophylaxis in caesarean section in Benin. Figure 5 from the guide (see appendix 4) displays the MUST-PIC recommendations for antibiotic prophylaxis in CS.

Procédure	Céfuroxime 750mg	Métronidazole 500 mg
Césarienne simple, programmée (membranes intactes)	1500mg (2 flacons) 30 minutes avant l'incision Dose unique	500mg (1 flacon) 30 minutes avant l'incision Dose unique
Césarienne compliquée (pendant le travail, rupture de la membrane)	1500mg (2 flacons) 30 minutes avant l'incision Dose unique	500mg (1 flacon) 30 minutes avant l'incision Dose unique

Figure 5: MUST-PIC antibiotic prophylaxis recommendations in CS

However, to strength these recommendations, a randomized clinical trial study can also be performed in women undergoing

caesarean section in Benin to compare the effectiveness of the potential antibiotics that can be used.

A collaborative paper written with the two other MUST-PIC researchers is in preparation for publication (Abstract in appendix 5).

The literature described the use of nudges to promote adherence to guidelines such as increasing the salience of information or incentives, understanding mapping, default choice, providing feedback, error reduction, and structuring complex choices [138]. Thaler et al. defined nudges as *"subtle changes in how choices are presented that can significantly influence a decision marker's behavior in predictable ways without restricting choices or changing economic incentives"*[139]. Implementing or identifying tailored nudges to Benin settings could be envisaged to raise adherence to guidelines. For example, a qualitative study (face-to-face interviews or focus groups) with concerned stakeholders in hospitals on the existing nudges described in the literature or in the process of seeking other nudges is a avenue of research.

3.3 Interventions to promote rational use of antibiotics

To promote the rational use of antibiotics, all the actors in the healthcare system have to be involved in a national policy of rational use of antibiotics. From our level, we suggest the following activities that could contribute to the promotion of rational use of antibiotics.

Thanks to the experience we acquired during our thesis, we plan to contribute to the rational use of antibiotics by sharing our results with health authorities, healthcare professionals, students, and people. Since we found a high rate of self-medication with antibiotics, we think that it will be useful to share these findings with private pharmacists in a specific workshop in the framework of the MUST-PIC incoming symposium in the next months of 2022. Since those private pharmacists are not involved in hospital activities, they might not feel concerned about Infection Prevention and Control. During this workshop, we will share data showing the importance of private pharmacists in IPC, especially in education and awareness people, and discuss with them to which extent they can be involved and participate.

We will work to have health authorities acknowledge the MUST-PIC antibiotic guide produced and promote its utilization in the hospitals. We are also going to participate in any project that can set up or boost the IPC activities like the development of the hospital pharmacy, and the nosocomial infection control committee.

In the health faculties, we are going to be involved in the interprofessional teaching of « Infection and Prevention Control » in Benin. This will be feasible because the University of Abomey Calavi is involved in the MUST-PIC project and the students of Faculté des Sciences de la Santé of Cotonou were motivated to participate in the micro-project conducted in Benin whose topic was in link with the MUST-PIC project.

We are also motivated to participate in national and global actions to promote the rational use of antibiotics as the GAP-AMR: Global Action Plan on Antimicrobial Resistance (WHO, 2015) whose goal is *"to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them".*

3.4 Interprofessional collaboration

Infection Prevention and Control activities are multidisciplinary works. According to the WHO, interprofessional collaboration is when *"multiple health workers from different professional backgrounds work together with patients, families, carers (caregivers), and communities to deliver the highest quality of care*" [140]. To make it works, all the stakeholders, healthcare professionals from the community, hospitals, and researchers have to work together. To this end, it will be useful to create a melting pot of exchange at the hospital, regional and national levels. The steps that can be taken include the listing of the competencies available; recognizing the place, role, responsibility, and importance of each stakeholder; implementing frequent communication between members; making discussions on specific each, learning from each other, and planning to improve the future (training). Implementing this steps could help to overcome some barriers of adherence to guidelines Patient safety and providing quality care are the cornerstone of this collaboration.

3.5. "One health approach" and avenues of research

The challenge of the rational use of antibiotics and prevention of AMR is, unfortunately, broader than the use of antibiotic prophylaxis. Several topics should be further studied such as the consumption of antibiotics (oral and injectable) at the hospital and national levels, and the consideration of antibiotic utilization in agriculture and veterinary. That means paying attention to the "one health approach" since it has an impact on antimicrobial resistance. In fact, according to the Centers for Disease Control and Prevention, *"One Health is a collaborative, multisectoral, and transdisciplinary approach – working at the local, regional, national, and global levels- with the goal of achieving optimal health outcomes by recognizing the interconnection between people, animals, plants and their shared environment*" [141].

4. Research perspectives

Although this thesis helped to provide numerous data in various topics, some research perspectives remain to be considered.

The analysis of the dispensation of the antibiotic in private pharmacies and the extent of the involvement of pharmacists in the private sector in Infection Prevention and Control is also relevant. The study of training curricula for health workers (anaesthetists, nurses, midwives, surgeons, pharmacists…) in Benin is also an important aspect since the quality of education is the key to good

practices. It could be about the proportion of the training dedicated to Infection Prevention and Control in health faculties. Thanks to the involvement of the University of Abomey Calavi in the MUST-PIC project, a pedagogic workshop was planned to take place in order to set up an IPC course in "Faculté des Sciences de la Santé.

At the hospital and national levels, the understanding of their organization and the planning of activities for Infection Prevention and Control could be some perspectives of research. Finally, having an idea of the integration of Benin national IPC actions into global ones could be useful.

Since the patient is a key participant in healthcare in Benin, particular attention has to be paid to his involvement. Patient education is a specific topic that can be investigated by the assessment of health literacy and analyse of the tools that can be provided to avoid irrational use of antibiotics after discharge.

As there is emerging in the literature, the implementation of the AMS in Benin has to be considered. The avenue of research can be "Implementation and evaluation of antimicrobial stewardship program in Benin" by making a review of the literature to highlight experiences in other low-income countries in order to provide tools for its implementation. Also, in a pilot study, AMS implementation can be analyzed in the specific context of Benin, evaluation of financial burden and the estimation of the needed competencies can also help the policymakers to make financial decisions and provide necessary training.

Several studies showed the importance of the clinical pharmacist in AMS management [122], [142]. It appears relevant to think about the development of clinical pharmacy in the hospitals in Benin. In 2020-2021, we participated in a work entitled "Pharmacie clinique et pays en développement" in the framework of a Master at UCLouvain (see appendix 6) to provide preliminary data. From the data of 47 countries included in this study, more than half (27 countries) did not have any activity of clinical pharmacy in their hospitals. In the countries clinical pharmacy was performed, antibiotics were the class of medicines that received attention. Through a qualitative study, the map of the needs of clinical pharmacist involvement in healthcare can be drawn to permit efficient collaboration in surgical wards. The data from the UCLouvain Master 's work in 2020-2021 can be a starting point for this study.

With regard to the evolution of antimicrobial resistance and the paucity of the development of new antibiotics, the WHO calls for alternative solutions such as providing antimicrobials from medical plants [143]. Medical plant utilization is cultural in Benin. Indeed, during interviews with patients, they mentioned some plants which supposed to have antibiotic activity. To provide evidence to their statements, we participated in a preliminary work titled "Les plantes aux propriétés antibiotiques du Bénin" in the framework of a Master at UCLouvain (see appendix 7). The objective was to cross the patients' statements with the literature to stress out a list of the medicinal plants which can be used in

research. It appeared that most of the plants indicated by the patients during interviews are described in the literature as having antimicrobial activities.

Among the microorganisms that the WHO called for finding medical alternative drugs, some of them were multiresistant germs isolated in the MUST-PIC study such as *Acinetobacter baumannii* and *Escherichia coli.* Based on the experience of the project VALTRAMAED in Benin (https://www.ares-ac.be/fr/cooperation-au-developpement/ pays-projets/projets-dans-le-monde/item/67-prd-renforcement-des-potentialites-de-valorisation-de-plantes-utilisees-en-medecine-traditionnelle-contre-les-infections-valtramed), where essential oils from medical plants were used in dermatologic infections, we think that research can also be make in this field.

In table 8, we displayed some perspective topics of research and suggestions of design of studies that can be used in each case.

Table 8: Topic of research perspectives **(1/2)**

Topic of research	**Proposals of design of study for the research**
Implementation and evaluation of an antimicrobial stewardship program (AMS)	Make an exploratory study to identify the challenges in the implementation of AMS. As it is perform in India, these challenges are multifactorial[128]. The exploratory study can help to highlight tailored challenges that can be face before or during the implementation. A literature review also can provide tools for implementation from example in low-income settings.
Economic evaluation of the AMS implementation in limited-resources	Perform a cost-effectiveness study to provide relevant data for implementation planification by policymakers

Table 8: Topic of research perspectives **(2/2)**

Topic of research	**Proposals of design of study for the research**
Clinical pharmacy in hospitals	Several studies described the importance of pharmacist in management of antibiotic in hospitals with positive outcomes such as the decrease of antibiotic consumption, cost and the reduction of the hospital stay[126], [144], [145]. In Benin, pharmacists are dedicated only for medicines (antibiotic) dispensation. They have to be more involve in its utilization in hospitals (support to medical teams) and provide relevant information to patients for discharge. In the case of research, pharmacist impacts on antibiotic use can be assess throughout the quality of antibiotic prophylaxis (adherence to the five conventional criteria), the availability of necessary antibiotics in each hospital by setting up a medical formulary in interprofessional process to optimize the antibiotic prophylaxis initiation.
Alternative antimicrobials from medical plants	A collaborative study in phytochemistry, pharmaceutical chemistry, pharmacognosy, toxicology, and microbiology could provide excellent results.

Conclusion

Conclusion

Infection and prevention control is a wide and key concept that has to be applied in any healthcare field. In the framework of this thesis, we worked to highlight its application in the ceasarean section in the context of the user fees exemption policy in Benin by analyzing the determinants of the rational use of antibiotics. To this end, we performed quantitative and qualitative studies on several aspects of the topic including different stakeholders of the healthcare system, and various types of hospitals. From the analysis of antibiotics usage to its quality control and exploration of different stakeholders' knowledge and beliefs (healthcare professionals, patients, policymakers), we noticed that number of determinants deserve room for improvement for patients' safety and quality care to reduce antimicrobial resistance occurrence and burden on the patient and public health.

To reach a rational use of antibiotics, collaborative work is essential. Patients have to be educated and aware to integrate fully with the challenge. There is a particular need for reinforcement of the healthcare professionals' capacities by training, multidisciplinary teamwork, and communication skills with patients and coworkers. The pharmacist, the specialist of the medicine is an uncourtounable actor in the rational use of antibiotics and has to be involved in research to provide relevant data, tools, and solutions for appropriate utilization of antibiotics. Hospital managers and policymakers have to provide adequate

environment, tools, and resources for the appropriate practice of Infection Prevention and Control.

Finally, the updating of data by funding research is important to keep all teams active and work continuously either at the local or global level for a better world.

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Appendices

Appendices

Appendix 1: Master in UAC on the assessment of the supply chain of antibiotics in hospitals.

RÉPUBLIQUE DU BÉNIN

MINISTÈRE DE L'ENSEIGNEMENT SUPÉRIEUR
ET DE LA RECHERCHE SCIENTIFIQUE

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UNIVERSITÉ D'ABOMEY-CALAVI

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FACULTÉ DES SCIENCES DE LA SANTÉ

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UNITÉ DE FORMATION ET DE RECHERCHE EN PHARMACIE

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Année : 2020 **N° 217**

ÉVALUATION DU SYSTÈME D'APPROVISIONNEMENT ET DISPONIBILITÉ DES ANTIBIOTIQUES UTILISÉS EN PROPHYLAXIE CHIRURGICALE DANS SIX HÔPITAUX DU BÉNIN

THÈSE

Présentée et soutenue publiquement pour obtenir le grade de

DOCTEUR EN PHARMACIE
DIPLÔME D'ETAT

Par

Alain Koovi BOCO

Né le 24 Septembre 1992 à Cotonou (République du Bénin)

DIRECTEUR DE THÈSE :

Maître de Conférences Agrégé **Loconon Y. Achille YEMOA**

CO-DIRECTEUR :

Maître Assistant **Jean-Marie TOKOUDAGBA**

RÉSUMÉ

Le système d'approvisionnement du médicament en milieu hospitalier est performant et fiable lorsqu'il assure la disponibilité et garantie la qualité du médicament. La disponibilité d'un médicament de qualité devient plus cruciale lorsqu'on parle d'antibioprophylaxie chirurgicale qui doit être conforme aux 5 critères conventionnels.

Depuis 2018, il est développé au Bénin dans six (06) hôpitaux, un Projet de Recherche pour le Développement (PRD) qui vise à contribuer à la réduction des infections associées aux soins (IAS) par la promotion de l'usage rationnel des antibiotiques et la pratique de l'hygiène hospitalière en chirurgie digestive et obstétrique. Dans sa première phase, il a été fait entre autres l'état des lieux sur l'antibioprophylaxie et a permis de noter des non conformités notamment dans le choix et le timing d'administration de l'antibiotique. Pour mieux comprendre ces non conformités, le projet s'est proposé à travers notre travail d'évaluer le système d'approvisionnement et la disponibilité des antibiotiques utilisés en prophylaxie.

Pour ce faire, nous avons adapté l'outil d'évaluation des indicateurs de la logistique et les outils d'évaluation du système logistique de John Snow qui a mise en place le PROJET USAID/DELIVER ; projet qui renforce les chaînes d'approvisionnement dont dépendent les systèmes de santé de certains pays.

Au terme de notre étude, nous avons constaté que le système d'approvisionnement en milieu hospitalier au Bénin est peu performant avec une disponibilité des antibiotiques utilisés en prophylaxie chirurgicale. Ces différentes situations ont une influence sur la pratique correcte de l'antibioprophylaxie et pourrait expliquer les non conformités ultérieurement observées. Les autorités hospitalières et nationales doivent prendre des mesures pour remédier à ces situations pour un système d'approvisionnement de qualité.

ABSTRAT

The hospital drug supply system is efficient and reliable when it ensures availability and guarantees the quality of the drug. The availability of a quality drug becomes more crucial when it comes to surgical antibiotic prophylaxis, which must meet the 5 conventional criteria.

Since 2018, a Research Project for Development (PRD) which aims to contribute to the reduction of healthcare associated infections (HAIs) by promoting the rational use of antibiotics and the practice of hospital hygiene in digestive and obstetric surgery in six (06) partner hospitals. In its first phase, among other things, the inventory of antibiotic prophylaxis was made and it was possible to note non-conformities, particularly in the choice and timing of administration of the antibiotic. To better understand these nonconformities, the project proposed itself through our work to assess the supply system and the availability of antibiotics used in prophylaxis.

To do this, we adapted the logistics indicator assessment tool and logistics system assessment tools of John Snow who set up the USAID / DELIVER PROJECT; project that strengthens the supply chains on which the health systems of some countries depend.

At the end of our study, we found that the hospital supply system in Benin performs poorly with a fair availability of antibiotics used in surgical prophylaxis. These different situations have an influence on the correct practice of antibiotic prophylaxis and could explain the nonconformities subsequently observed. Hospital and national authorities must take action to remedy these situations for a quality supply system.

Appendix 2 : Hand hygiene in surgery in Benin: opportunities and challenges **(Abstract)**

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Antimicrobial Resistance and Infection Control

RESEARCH Open Access

Hand hygiene in surgery in Benin: opportunities and challenges

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Abstract

Background: Hand Hygiene (HH) has been described as the cornerstone and starting point in all infection control. Compliance to HH is a fundamental quality indicator. The aim of this study was to investigate the HH compliance among Health-care Workers (HCWs) in Benin surgical care units.

Methods: A multicenter prospective observational study was conducted for two months. The World Health Organization (WHO) Hand Hygiene Observation Tool was used in obstetric and gastrointestinal surgery through six public hospitals in Benin. HH compliance was calculated by dividing the number of times HH was performed by the total number of opportunities. HH technique and duration were also observed.

Results: A total of 1315 HH opportunities were identified during observation period. Overall, the compliance rate was 33.3% (438/1315), without significant difference between professional categories (nurses =34.2%; auxiliaries =32.7%; and physicians =32.4%; $p = 0.705$). However, compliance rates differed ($p < 0.001$) between obstetric (49.4%) and gastrointestinal surgery (24.3%). Generally, HCWs were more compliant after body fluid exposure (54.5%) and after touching patient (37.5%), but less before patient contact (25.9%) and after touching patient surroundings (29.1%). HCWs were more likely to use soap and water (72.1%) compared to the alcohol based hand rub solution (27.9%). For all of the WHO five moments, hand washing was the most preferred action. For instance, hand rub only was observed 3.9% after body fluid exposure and 16.3% before aseptic action compared to hand washing at 50.6 and 16.7% respectively. Duration of HH performance was not correctly adhered to 94% of alcohol hand rub cases (mean duration 9 ± 6 s instead of 20 to 30 s) and 99.5% of hand washing cases (10 ± 7 s instead of the recommended 40 to 60 s). Of the 432 HCWs observed, 77.3% followed HH prerequisites (i.e. no artificial fingernails, no jewellery). We also noted a lack of permanent hand hygiene infrastructures such as sink, soap, towels and clean water.

Conclusion: Compliance in surgery was found to be low in Benin hospitals. They missed two opportunities out of three to apply HH and when HH was applied, technique and duration were not appropriate. HH practices should be a priority to improve patient safety in Benin.

Keywords: Hand hygiene, Alcohol based hand rub, Hand washing, Surgery, Observation

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Appendix 3: Audit of antibiotic prophylaxis practice in visceral surgery in 5 hospitals in southern Benin **(Abstract).**

Audit of Antibiotic prophylaxis practice in visceral surgery in 5 hospitals in southern Benin.

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ABSTRACT

Background: Appropriate use of surgical antibiotic prophylaxis (SAP) is essential to prevent surgical site infection. In Benin, in the absence of a defined and known local guideline, practitioners often refer to French standards. However, health care workers' compliance with SAP measures and recommendations is unknown.

Aim: To audit compliance in southern Benin with five conventional criteria for SAP practices in visceral surgery.

Methods: Data were prospectively collected in visceral surgery wards of 5 hospitals in Benin. During 4 months, SAP was assessed with five conventional criteria (antibiotic prophylaxis indication, choice of molecule, dosage, timing, and duration) among patients admitted for class 1 or 2 surgery according to Altemeier's classification. Three international guidances were **considered as** a reference: SFAR, WHO, and the directive produced jointly by ASHP, IDSA, SIS, and SHEA (referred to below as ASHP).

Finding: In 68 interventions observed, overall compliance was respectively 0 (0.0%), 0 (0.0%), 1 (1.5%) according to SFAR, WHO, and ASHP. Compliance with indication was observed in SFAR: 47 (69.11%), WHO: 65 (95.6%) and ASHP: 65 (95.6%) cases. However, the molecules chosen differed from the guidelines: SFAR compliance in 3 (4.4%), WHO 2 (2.9%), and ASHP 2 (2.9%) cases. Ceftriaxone and amoxicillin + clavulanic acid were the most used molecules (21 cases). Compliance with the dosage of the molecule was observed in SFAR: 20 (29.4%), WHO: (-), and ASHP 49 (72.0%). The timing was compliant respectively in 9 (13.2%), 47 (69.1%), and 45 (66.2%). And finally, compliance with a duration of antibiotic prophylaxis was observed in SFAR: 16 (23.5%), WHO: 13 (19.1, %) and ASHP: 17 (25.0%).

Conclusion: The compliance rate of SAP according to five conventional criteria in visceral surgery services was very low. It is necessary to implement appropriate SAP guidance based on local epidemiology.

Keywords: Antibiotic prophylaxis -Audit - Visceral surgery - compliance

Appendix 4: Antibiotic guide made after Delphi process.

Appendix 5: Abstract of Delphi process study

Using the modified Delphi method to develop Surgical Antimicrobial prophylaxis and surgical site infections in Benin

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Background: Improving surgical antibiotic prophylaxis (SAP) practices for the reduction of surgical site infections (SSIs) remains challenging in low-middle-income countries, especially in the absence of local guidelines. We aimed to implement guidelines for the rational use of antibiotics in surgical prophylaxis in gastrointestinal surgery and maternity wards in Benin.

Methods: The Delphi's study involved one round of consensus building between February and April 2021. The expert panel included 14 experts from Benin and Belgium: microbiologists, pharmacists, surgeons, gynecologists, hygienists, and infectious diseases specialists. Guidelines on surgical antimicrobial prophylaxis were developed using recent results on the antimicrobial susceptibility of bacteria isolated in surgical site infections from six hospitals in Benin and the availability of antibiotics in Benin. In addition, some recommendations about the treatment of SSIs were included: specific cases of gastrointestinal interventions, and simple or complicated cases of caesarean section. The guidelines are included in a booklet providing general information about

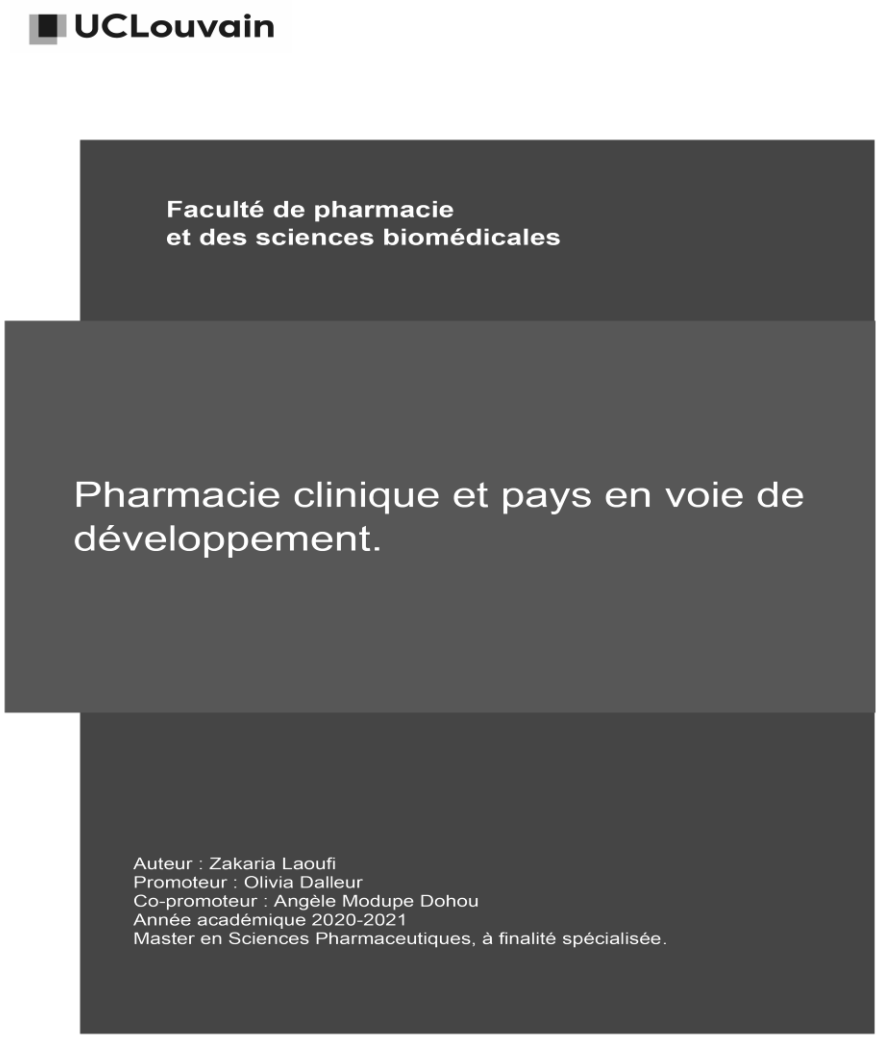
antibiotics and antimicrobial resistance. The panel used a four-level Likert-type scale to record agreement or disagreement with antibiotics schemes for prophylaxis and SSIs treatment. Consensus was established at 70% of agreement by experts and an upper quartile ≥3.25 for an item.

Results: The national guideline panel reached a consensus on eleven essential combinations of antibiotics for SAP and SSIs treatment. Evaluation of the first round showed that > 90% consensus had been reached on all the statements on the regimen that should be applied for surgical antimicrobial prophylaxis and SSIs treatment. Experts suggested minor modifications to the wording and the content of the booklet. A second version of the booklet including the guidelines was sent to the experts for final approval.

Conclusions: Through validation of the contents based on experts' consensus, it was possible to agree on an essential approach to improving the practices of surgical antimicrobial prophylaxis in hospitals in Benin. As valuable feedback was provided by the multidisciplinary team, this consensus guideline will help to standardize the use of antibiotics in surgical wards.

Keywords: Delphi Process - surgical site infection - surgical antimicrobial prophylaxis - antibiotics guideline - Benin.

Appendix 6: Clinical Pharmacy and low-income countries



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L'objectif de notre travail est de documenter la présence de la pharmacie clinique par pays et d'identifier les activités ciblées sur le patient et les activités non individualisées.
Sur la base des activités non individualisées, nous voulions décrire les principales classes médicamenteuses qui font l'objet d'usage irrationnel, les outils pour promouvoir la sécurité des médicaments et les outils utilisés pour la formation des pharmaciens dans les pays en voie de développement.

Méthodes : La recherche bibliographique a été effectuée conformément aux recommandations PRISMA dans les bases de données suivantes : PubMed, Cochrane Library et Impact Pharmacie.
Pour les 47 pays en voie de développement, les mots clés suivants ont été utilisés : pharmacist, clinical pharmacy et pharmaceutical care.
Nous avons classé les articles obtenus selon les deux familles : les activités individualisées et les activités non individualisées décrites par M. Cillis.

Résultats : Nous avons identifié 82 activités de pharmacie clinique décrites dans 75 articles. 17 tâches dans la famille des activités individualisées et 65 tâches dans les activités non individualisées. Sur les 47 pays en voie de développement, 27 n'ont aucune activité de pharmacie clinique.
Les classes médicamenteuses qui font l'objet d'usage irrationnel sont les antibiotiques, les antipaludiques, les médicaments du système cardiovasculaire, les antidiabétiques et les antiasthmatiques. La sous-déclaration des effets indésirables par le personnel médical est une pratique répandue dans les pays en voie de développement.
Les outils de formation pour les pharmaciens ont été décrits dans cinq publications. Les lignes directrices, les centres d'information, les programmes et les questionnaires éducatifs sont les principaux outils utilisés.

Conclusion : Les activités de pharmacie clinique sont distribuées de manière hétérogène dans les pays en voie de développement. Les différentes tâches réalisées par le pharmacien clinicien ont montré un bénéfice incontestable. Les mauvaises pratiques contribuent à alourdir les dépenses des soins de santé qui sont déjà limitées dans un contexte économique fragile. Promouvoir la formation des pharmaciens cliniciens est la priorité pour le développement de la pharmacie clinique.

Mots clés : pharmacie clinique, pharmacien, activités individualisées, activités non individualisées, pays en voie de développement.

The aim of this study is to investigate the presence of clinical pharmacy by country and to identify patient-centered activities and non-patient centered activities.

Based on non-patient centered activities, we document the most common drugs involved in therapy problems, the tools used to promote drug safety and for the training of pharmacists in developing countries.

Methods: The literature search was conducted according to PRISMA guidance. The database included: PubMed, Cochrane Library, and impact pharmacie. For the 47 developing countries, the following MeSH were used: pharmacist, clinical pharmacy, and pharmaceutical care. We classified the studies obtained on patient-centered activities and non-patient centered activities described by M. Cillis.

Results: In this study, a total of 82 clinical pharmacy activities were identified in 75 studies. 17 tasks in the patient centered activities and 65 tasks in the non-patient centered activities. Of 47 developing countries, 27 had no clinical pharmacy activity.

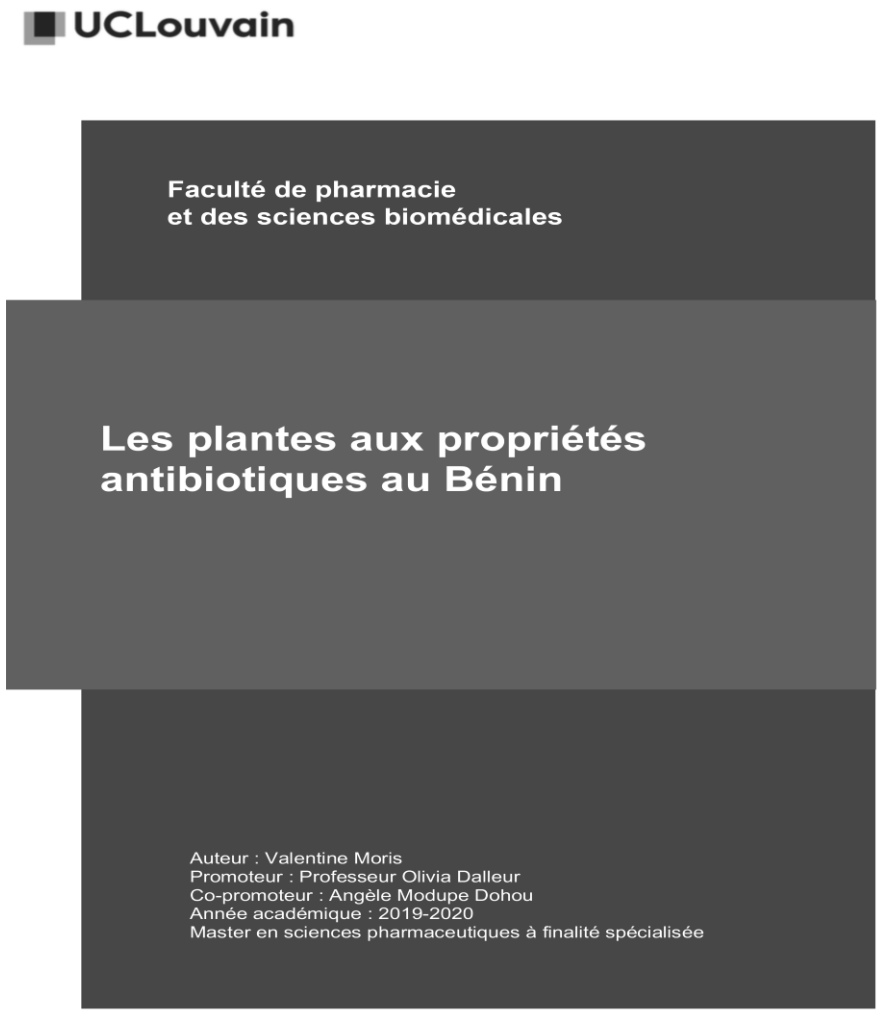
The drug classes involved in the drug therapy problems are antibiotics, antimalarials, cardiovascular drugs, antidiabetics and antiasthmatic drugs. The underreporting of side effects by healthcare professionals is a widespread practice in developing countries.

Training tools for pharmacists have been described in five articles. Guidelines, information centers, educational programs, and questionnaires are the main tools used.

Conclusion: Clinical pharmacy activities are heterogeneously distributed in developing countries. Several activities performed by clinical pharmacists have shown unquestionable benefits. Inappropriate practices contribute to increased health care expenditures, which are already limited in a fragile economic context. Promoting the training of clinical pharmacists is the priority for the development of clinical pharmacy.

Keywords : Clinical pharmacy, pharmacist, patient centered activities, non-patient centered activities, developing countries.

Appendix 7: Benin medical antibiotic plants



Résumé :
L'usage abusif et l'utilisation inappropriée d'antibiotiques ont conduit à une augmentation des résistances des bactéries envers ceux-ci. Le traitement de bactéries multirésistantes devient donc de plus en plus compliqué. Cela nous oblige à trouver des alternatives, les plantes médicinales pourraient être un bon choix car elles constituent une grande réserve de substances actives. Ce mémoire a pour objectif de décrire des plantes utilisées en médecine traditionnelle au Bénin pour traiter les infections bactériennes. Nous avons compilé les informations disponibles qui évaluent les propriétés antibactérienne utilisées au Bénin pour les 9 plantes suivantes : A*nthocleista vogelii, Anthocleista djalonensis, Ocimum gratissimum, Crateva adansonii, Senna siamea, Psidium guajava, Momordica charantia, Parkia biglobosa* et *Moringa oleifera* car elles semblent mieux décrites par la littérature consultée. Après avoir déterminé les pathologies pour lesquelles elles sont utilisées en médecine traditionnelle et les éventuelles propriétés antibiotiques confirmées par la science, le but est également de cibler des métabolites secondaires responsables de cette activité. Enfin, il vise aussi à poser des pistes pour pouvoir peut-être proposer aux Béninois une médecine plus accessible que la médecine allopathique et identifier des alternatives potentielles aux antibiotiques présents dans la médecine conventionnelle.

Abstract :
The overuse and improper use of antibiotics has led to an increase in bacterial drug resistance. The treatment of multidrug-resistant bacteria is therefore becoming increasingly complicated. This forces the scientific community to find alternatives. The medicinal plants could be a good choice because they constitute a large reserve of active substances.
The present thesis aims to describe the plants used in traditional medicine in Benin to treat bacterial infections. We have compiled the available information which assesses the antibacterial properties used in Benin for the following 9 plants: *Anthocleista vogelii, Anthocleista djalonensis, Ocimum gratissimum, Crateva adansonii, Senna siamea, Psidium guajava, Momordica charantia, Parkia biglobosa* and *Moringa oleifera* as they they were deeper described in the consulted literature.
After determining the pathologies for which they are used in traditional medicine and the possible antibiotic properties confirmed by science, the goal was also to identify the secondary metabolites responsible for this activity. Finally, it paves the way in order to perhaps be able to offer to the Beninese people a more accessible medicine than allopathic medicine and identifying potential alternatives to the regular antibiotics proposed in the conventional medicine.

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Curriculum vitae

Curriculum vitae

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Education

2016-2022	PhD in : - biomedical and pharmaceutical sciences, Clinical Pharmacy research group, UCLouvain - Ecole doctoral Sciences de la santé, UAC
2009-2010	Master complémentaire en pharmacie d'hôpital, UCLouvain
2001-2008	Doctorat d'état en pharmacie, UAC

AWARDS

3è prix du jury et prix du public au Concours national "Ma thèse en 180 secondes" UAC, Bénin 2018.

CERTIFICATES AND COURSES

Certificat d'apprentissage collectif de la chaîne d'approvisionnement pour la santé, Bee skilled-FAAL, online 2022.

Certificat en MOOC on Implementation Research (IR) with a focus on Infectious Diseases of Poverty (IDP), TDR-OMS, online 2020

Cours interuniversitaire de gestion de l'antibiothérapie, Bruxelles 2017

COMMUNICATIONS IN RELATIONSHIP WITH THIS THESIS

Scientific publications

Antibiotic Usage in Patients Having Undergone Caesarean Section: A Three-Level Study in Benin. Angèle Modupè Dohou, Valentina Oana Buda, Loconon Achille Yemoa, Severin Anagonou, Françoise Van Bambeke, Thierry Van Hees, Francis Moïse Dossou and Olivia Dalleur. Antibiotics 2022, 11, 617. https://doi.org/10.3390/antibiotics11050617

Assessment of the Quality of Injectable Antibiotics in Benin. Angèle Modupè Dohou*, Achille Loconon Yémoa, Dodji Boris Aurel Guidan, Seyive Hélène Solange Ahouandjinou, Ahmed Amoussa, Francis Moïse Dossou, Roland Marini Djang'eing'a, and Olivia Dalleur. American Journal of Tropical Medecine and Hygiene, June 2022, https://doi.org/10.4269/ajtmh.21-0844

Healthcare Professionals' Knowledge and Beliefs on Antibiotic Prophylaxis in Cesarean Section: A Mixed-Methods Study in Benin. Angèle Modupè Dohou*, Valentina Oana Buda, Severin Anagonou, Françoise Van Bambeke, Thierry Van Hees, Francis Moïse Dossou and Olivia Dalleur. Antibiotics 2022, 11, 872. https://doi.org/10.3390/antibiotics11070872

Oral communications

Analyse de l'utilisation des antibiotiques en césarienne au Bénin. 3è journées scientifiques médicales, Pharmaceutiques et Odonto-stomatologiques, Ouagadougou, Burkina Faso - Janvier 2018.

Assessment of the quality of injectable antibiotics in Benin, 2è congrès de la Société Ouest Africaine de Pharmacie Galénique et Industrielle, Ouagadougou, Burkina Faso 2021.

Posters presentation

Antibioprophylaxis in cesarean section: what are the current practices in four hospitals in Benin? International conference on prevention and infection control, Genève, Suisse - June 2017.

Hand hygiene to prevent healthcare-associated infections: investigation in Beninese settings, 4è Journées Scientifiques du CAMES, Ouidah, Benin - December 2019.

Antibioprophylaxis in cesarean section in Benin: challenges for practice improvement, International conference, Institute of Healthcare Improvement, Online November 2020.

The decision-making process in health policy impacts clinical practices: a qualitative study, 26th congress of European Association Hospital Pharmacists, Vienne, Austria - Mars 2022.

Delphi process to develop guidelines for rational use of antibiotics in surgery: an experience in a low-income country, European Society of Clinical Pharmacy, Zurich, Suisse - Avril 2022.

Summary

Summary

The discovery of antibiotic change the therapeutic story and provided a hope for humanity. After years, its inappropriate utilization drove in a global public health disaster: the antimicrobial resistance with a threat of a "post-antibiotic era". Urgent action is need to avert this threat. Several strategies were set up to fight the problem such as Infection Prevention and Control which aims to improve the use of antibiotic. To make it possible, it is essential to have available the data of antibiotic consumption and antimicrobial resistance. This work identified the bottlenecks of the rational use of antibiotics in Benin in the context of the user fees exemption policy with a national free kit containing the required materials and medicines (including antibiotics) for the intervention.

How antibiotics are used?

Through a prospective observational study and a medication history in patients undergoing caesarean section in four hospitals in south Benin, we analyzed the utilization of antibiotics before, during, and after surgical intervention. More than half (57.6%) of 141 patients included used to use antibiotics often for unknown reasons. For prophylaxis, Only 31.2% of practices conformed to conventional criteria. Almost all patients received broad-spectrum antibiotics after caesarean section in the absence of documented infection. It results in misuse, overuse, and underuse of antibiotics in the population studied.

Why antibiotics are used inappropriately?

From two different studies, some findings helped to identify the reasons for the inappropriate utilization. Firstly, in a mixed-method study performed on healthcare professionals in the hospitals, the assessment of the level of knowledge of antibiotic prophylaxis showed that only 15.2% of 33 participants gave the 5 good responses to the 5 conventional criteria. The mean level of knowledge of antibiotic prophylaxis criteria was 3.3 out of 5. In data that emerged from the 19 interviews, healthcare professionals expressed an absence of confidence in the antibiotics in the kit and some general disagreement with the policy. In addition to the absence of appropriate infrastructure for surgical intervention, the unavailability of antibiotics in the hospital pharmacies and in the kit, interviewees acknowledged the lack of communication between healthcare professionals and between different departments (operating area and hospitalisation). They also pointed out the lack of their involvement in the policy formulation. The major determinant of the inappropriate antibiotic prophylaxis practices was the patient behavior in terms of refusal to buy prescribed antibiotics because of the user exemption policy and/or the lack of money.

In another qualitative study, we performed 30 interviews with patients after their intervention to explore their knowledge of healthcare associated infections and antibiotic utilization. It results in that patients had appreciate knowledge of hospital-acquired-infections and their means of transmissions but reported erroneous

indication of antibiotics, described its use in context that do not have any link with infectious diseases (pain, malaria). It also appeared a lack of communication around care between patients and healthcare professionals with consequence of suboptimal medical information provided to patients.

What about the chemical quality of the antibiotics in the kit and the process of the policy formulation?

The antibiotics used in prophylaxis in Benin hospitals were submitted to a panel of chemical analysis. A proportion of 85% of them conform to the quality requirements, 15% failed visual inspection and active ingredient quantification tests.

The interviews conducted in 6 stakeholders involved in the policy formulation, it emerged that some concerned actors were not involved in the policy formulation and the antibiotics were chosen in a mixed-consensual context without scientific evidence-based considerations.

The analysis of the findings emerged from our studies showed that the bottlenecks of the rational use of antibiotics are in all levels of the healthcare system (healthcare professionals, patients and policymakers)

Rational use of antibiotics be possible?

Considering the burden the inappropriate use of antibiotics induces for patient and public health, it is imperative to implement

actions to improve the use of antibiotic. Based on our findings and the literature in field, a program named antimicrobial stewardship helps hospitals to coordinate a set of actions aimed at promoting the prudent use of antimicrobials, with the ultimate goal of optimizing clinical outcomes while minimizing unfavorable consequences including resistance selection as well as adverse drug reactions. This program includes various actions for all actors of the healthcare system such as patient education, healthcare professional training, involvement in infection prevention and control strategies, and policymakers' commitment in terms of providing needed infrastructures and resources.

For the specific setting of Benin, a tailored concept of this kind of program has to be thought of in a collaborative and multidisciplinary approach for rational use of antibiotics.

Résumé

La découverte de l'antibiotique a changé l'histoire de la thérapeutique et a donné un espoir à l'humanité. Après des années, leur utilisation inappropriée a conduit à un désastre mondial en matière de santé publique: la résistance antimicrobienne avec la menace d'une "ère post-antibiotique". Il est urgent d'agir pour écarter cette menace. Plusieurs stratégies ont été mises en place pour combattre le problème, comme la prévention et le contrôle des infections, qui vise à améliorer l'utilisation des antibiotiques. Pour y parvenir, il est essentiel de disposer des données sur la consommation d'antibiotiques et la résistance aux antimicrobiens. Ce travail présente une vue d'ensemble de l'utilisation des antibiotiques dans la césarienne et identifie les goulots d'étranglement d'une utilisation rationnelle des antibiotiques au Bénin dans le cadre de la politique de gratuité de la césarienne qui met à disposition un kit national gratuit, contenant le matériel et les médicaments nécessaires (y compris les antibiotiques) pour l'intervention.

Comment les antibiotiques sont-ils utilisés ?

Par le biais d'une étude observationnelle prospective et d'une anamnèse médicamenteuse auprès des patientes subissant une césarienne dans quatre hôpitaux du sud du Bénin, nous avons analysé l'utilisation des antibiotiques avant, pendant et après l'intervention chirurgicale. Plus de la moitié (57,6 %) des 141

patientes incluses avaient l'habitude d'utiliser des antibiotiques, souvent pour des raisons inconnues avant leur admission à l'hôpital. Pour la prophylaxie, seulement 31,2% des pratiques étaient inappropriés aux critères conventionnels avec des non-conformités plus fréquentes pour le choix de la molécule, la dose à administrer et la durée d'administration. Presque toutes les patientes ont reçu des antibiotiques à large spectre après la césarienne en l'absence d'infection documentée. Il en résulte une mauvaise utilisation, une surutilisation et une sous-utilisation des antibiotiques dans la population étudiée.

Pourquoi les antibiotiques sont-ils utilisés de manière inappropriée ?

À partir de deux différentes études, certains résultats ont permis d'identifier les raisons de cette utilisation inappropriée.

Premièrement, dans une étude à méthode mixte réalisée au sein des professionnels de santé des hôpitaux, l'évaluation du niveau de connaissance de l'antibioprophylaxie a montré que seuls 15,2% des 33 participants ont donné les 5 bonnes réponses aux 5 critères conventionnels. Le niveau moyen de connaissance des 5 critères de l'antibioprophylaxie était de 3,3 sur 5. Des données issues des 19 entretiens individuels et focus group, les professionnels de santé ont exprimé une absence de confiance aux antibiotiques contenus dans le kit et un désaccord général avec la politique de gratuité. Outre l'absence d'infrastructures appropriées pour les interventions chirurgicales, l'indisponibilité des antibiotiques dans les pharmacies hospitalières et dans le kit, les personnes interrogées

ont reconnu le manque de communication entre les professionnels de santé et entre les différents services (bloc opératoire et hospitalisation). Ils ont également souligné le manque de leur implication dans la formulation de la politique de gratuité. Le principal déterminant des pratiques inappropriées d'antibioprophylaxie exprimé par les professionnels de santé était le comportement du patient (ou son accompagnant), qui refusait d'acheter les antibiotiques prescrits en raison de la politique de gratuité et/ou du manque d'argent.

Dans une autre étude qualitative réalisée avec 30 patients après leur intervention nous avons exploré leur connaissance des infections associées aux soins et de l'utilisation des antibiotiques. Il en ressort que les patients avaient une connaissance appréciée des infections nosocomiales (mais pas précisément des infections associées aux soins) et de leurs modes de transmission mais rapportaient des indications erronées des antibiotiques, décrivaient leur utilisation dans des contextes qui n'ont pas de lien avec des maladies infectieuses (douleur, paludisme). Il est également apparu un manque de communication autour des soins entre les patients et les professionnels de santé avec pour conséquence une information médicale sous-optimale fournie aux patients.

Qu'en est-il de la qualité chimique des antibiotiques contenus dans le kit et du processus de formulation de la politique ?

Les antibiotiques utilisés en prophylaxie dans les hôpitaux du Bénin ont été soumis à un panel d'analyses chimiques. Une

proportion de 85% d'entre eux était conforme aux exigences de qualité, 15% ont échoué à l'inspection visuelle et aux tests de quantification de principes actifs.

Des entretiens menés auprès de 6 acteurs impliqués dans la formulation de la politique, il ressort que certains acteurs concernés par la césarienne n'ont pas été impliqués dans la formulation de la politique et que les antibiotiques ont été choisis dans un contexte de consensus mitigé sans considération de preuves scientifiques.

L'analyse des résultats de nos études a montré que les goulots d'étranglement de l'utilisation rationnelle des antibiotiques se situent à tous les niveaux du système de santé (professionnels de santé, patients et décideurs politiques).

L'utilisation rationnelle des antibiotiques est-elle possible?

Compte tenu du fardeau que représente l'utilisation inappropriée des antibiotiques pour la santé des patients et la santé publique, il est impératif de mettre en œuvre des actions visant à améliorer l'utilisation des antibiotiques. Sur la base de nos résultats et de la littérature, un politique hospitalière puis nationale d'utilisation rationnelle des antibiotiques pourrait être envisagée. Il est décrit de plus en plus le concept d' « antimicrobial stewardship » qui permet aux hôpitaux de coordonner un ensemble d'actions visant à promouvoir l'utilisation prudente des antimicrobiens, dans le but ultime d'optimiser les résultats cliniques tout en minimisant les conséquences défavorables, notamment la sélection de la résistance ainsi que les effets indésirables des médicaments. Ce

programme comprend diverses actions incluant tous les acteurs du système de santé. Ces actions sont entre autres l'éducation des patients, la formation des professionnels de santé ainsi que leur implication dans les stratégies de prévention et de contrôle des infections, et l'engagement des décideurs politiques en termes de fourniture des infrastructures et des ressources nécessaires. Pour le contexte spécifique du Bénin, un concept adapté de ce type de programme doit être pensé dans une approche collaborative et multidisciplinaire pour une promotion de l'usage rationnel des antibiotiques.

Abstract

The inappropriate utilization of antibiotics drove to a global public health threat: the antimicrobial resistance. Several strategies were set up to fight the problem such as Infection Prevention and Control which aims to improve the use of antibiotic. Our work identified the bottlenecks of the rational use of antibiotics in Benin in the context of the user fees exemption policy in caesarean section with a national free kit.

The findings of our five studies showed:

- a misuse, overuse, and underuse of antibiotics before, during and after caesarean section,
- a low level of knowledge of antibiotic prophylaxis in healthcare professionals, a lack of confidence in the kit, and some general disagreement with the policy,
- some cases of overdosage of active ingredient,
- a mixed knowledge of antibiotics and their utilization by patients,
- a low involvement of end-implementers during the policy formulation, a mixed-consensual context without scientific evidence-based considerations in the choice of antibiotics in the kit.

The analysis of these findings revealed that the bottlenecks of the rational use of antibiotics were in all levels of the Benin healthcare system (healthcare professionals, patients and policymakers). Considering the burden the inappropriate use of antibiotics induces for patient and public health, it is imperative to implement actions to improve the use of antibiotics.

Based on the literature, a program named "antimicrobial stewardship" permits to coordinate a set of actions for promoting the prudent use of antimicrobials, with the ultimate goal of optimizing clinical outcomes while minimizing unfavorable consequences including resistance selection as well as adverse drug reactions. This program includes various actions for all actors of the healthcare system such as patient education, healthcare professional training and involvement in Infection Prevention and Control strategies, and policymakers' commitment. The implementation of this kind of program in hospitals could help to promote the rational use of antibiotics in Benin.