UNIVERSITÀ CATTOLICA del Sacro Cuore

ALTEMS
ALTA SCUOLA DI ECONOMIA
E MANAGEMENT DEI SISTEMI SANITARI

FEASIBILITY STUDY OF THE NEW TOILETRY MEDICAL DEVICE BY PLANUS SPA

Final Scientific Report
Rome, 17/01/2022

Prof. Americo Cicchetti
Scientific Responsible of the Project

Largo Francesco Vito, 1 - 00168 Roma - Italy - tel. +39 06.3015.4090; fax +39 06.3015.5779 - e-mail: altems@rm.unicatt.it - web: http://altems.unicatt.it

Preface

In Italy and in Europe, medical devices sector has a great importance in health care due their contribute to the improvement of people's level of health through the development of innovative solutions for diagnosis, prevention, treatment and rehabilitation.

The development of biomedical technologies in recent years has led a revolution in diagnostic and therapeutic approaches in many medical and surgical disciplines. It requires significant investments in research and development by – but not only – industries.

In the field of medical devices, industries need support by healthcare professionals in order to acquire clinical data for the evaluation of the performance, safety and efficacy, before and after commercialization.

It must be recognized the constant and considerable commitment provided by investigators, health facilities, Ethics Committees and the Competent Authority such as the Ministry of Health aimed to protect the health of patients enrolled in clinical trials and the promotion of clinical research in Italy.

These aspects are particularly important considering the emergency we have experienced in recent months. The management of COVID-19 has proven to be extremely challenging for hospitals and health systems, but at the same time it has confirmed the universal value of health, its nature as a fundamental public good. The emergency despite its dramatic nature can be an engine for Italian NHS change and renaissance, strengthening technological innovation for care and treatment of patients.

Scientific Responsible
Prof. Americo Cicchetti

Disclosure

This work was made by the support of Planus SPA. The results published were not contingent on sponsor approval. Therefore, the results reported represent the views of the authors and not necessarily those of the sponsors.

Acronyms

AMR Antimicrobial Resistance
BIA Budget Impact Analysis
CIP Clinical Investigation Plan
CRAB Carbapenemase-resistant Acinetobacter baumannii
CRE Carbapenemase-resistant Enterobacteriaceae
CRPsA Carbapenem-resistant pseudomonas aeruginosa
EBV Ebola virus
ECDC European Centre for Disease Prevention and Control
ESBL Enterobacteriaceae Extended Spectrum Beta-Lactamase
ESBL Extended-spectrum beta-lactamase
EUnetHTA European Network Health Technology Assessment
GCP Good Clinical Practice Standards
GDG Guideline Development Group
(HCAI) Healthcare-associated infections
IPC Infection Prevention and Control
ISS Istituto superiore di sanità
KPC Klebsiella pneumoniae carbapenemase-producer
MDR-GNB Multidrug-resistant Gram-negative bacteria
MRSA Methicillin-resistant Staphylococcus aureus
ODV Organismo di vigilanza (Supervisory Board)
PDF Patient Discharge Form
PICO Population, Intervention, Comparator, Outcome
PMCF Post marketing studies
PMS Post-market medical surveillance
SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus-2
SoC Standard of Care
SSN National Health Service
VRE Vancomycin-resistant Enterococci
WHO World Health Organization

Summary

Contributions

Authors

Americo Cicchetti[1], Giovanna Elisa Calabrò[2], Alessandra Fiore[3], Filippo Rumi[3], Michele Basile[3], Fabio Pattavina[4], Francesca Orsini[3], Alessia Pierotti[3], Maria Giovanna Di Paolo[3].

[1]Director of the Alta Scuola di Economia e Management dei Servizi Sanitari (ALTEMS) Università Cattolica del Sacro Cuore, Rome, Italy.
[2]Section of Hygiene, University Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy.
[3]Alta Scuola di Economia e Management dei Servizi Sanitari (ALTEMS) - Università Cattolica del Sacro Cuore, Rome, Italy.
[4]U.O.C. Section of Hygiene, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.

Corresponding Author
Alessandra Fiore
(alessandra.fiore@unicatt.it)

Executive summary

Background

In sanitary facilities, the aerial diffusion of potentially pathogenic microorganisms present in faecal material during toilet flushing suggests a highter frequency of disinfection processes. Healthcare-associated infections (HCAI) are caused by bacteria, viruses or fungi, conventional or opportunistic pathogens. Most of the time they are multi-resistant and not clinically manifest beforea variable period ranging from 30to 90 days after admission. Toilé is a first level risk class toilet capable of sucking the air directly from the toilet bowl during use, piping it outside the building through the sewer line. Its operation prevents the diffusion of microorganisms into the air after patients' physiological functions , and consequently, its adoption could reduce the high impact of HCAI.

Objectives and Methods

In order to understand the impact that Toilé device could have on the spread of infections in hospital settings, a literature review was conducted to identify studies oriented towards the identification of pathogens capable to be spread into the environment after toilet uses. At the same time, a manual search of the main guidelines on the subject was carried out, useful for a further framing of the subject under analysis. The report was constructed following the methodology defined by the Core Model® framework established within the European Network for Health Technology Assessment (EUnetHTA) (version 3.1). A Budget Impact Analysis (BIA) was conducted in order to evaluate the economic impact on Italian NHS.

Results

<u>Literature Review</u>

The results from literature review, according to the inclusion criteria considered, have included 10 articles and 4 guidelines The clinical studies have identified pathogens/viruses/bacteria capable be spread in the air during the use of WC . The results are reported in a table describing the type of microorganism identified, the population considered (healthcare workers and/or inpatients) and the sanitization system analysed in the study (surface disinfection and/or air ventilation/purification system).

From the summary of the guidelines, it emerges that the cleanliness of the environment and the maintenance of the built environment is a key element in preventing HCAI and pathogens cross-transmission. In addition, the management of the air conditioning and ventilation system of the environment where the toilet is installed must be adapted to the characteristics of the system and use of the rooms. It has also been assessed the risk for healthcare workers who come in contact with pathogens in hospital toilets.

<u>Economic evaluation</u>

According to PDF data from 2019, there are 499,809 patients in our country with at least one nosocomial infection. (PDF, 2019) The economic evaluation conducted by ALTEMS estimates the introduction of Toilé in the Italian care setting; it is associated with resource savings in each year of analysis. In particular, the saving is incremental and reaches its peak in the third year of observation with a deviation. Compared to the scenario in which is not provided the use of this medical device, the saving is equal to - € 9,905,131, which is pair to an overall saving in the three years under analysis of € 20,285,164. According to that, a wider diffusion of this device in the

Italian hospital setting is desirable. Toilé, in fact, has the purpose of preventing the spread of viruses and bacteria through the toilets, inserting itself in a context of safety at work, for health workers, and contrasting resistant bacteria. Its operation prevents the spread of viruses and bacteria in the air after the completion of the physiological functions of patients and consequently its adoption could reduce the high impact of nosocomial infections, allowing a progressive saving for the NHS.

Clinical Protocol

Based on what has been defined in the New Regulation (EU) 2017/745, the clinical investigation plan and the clinical protocol have been defined in order to support the Company to define possible clinical study aimed at assessing the risk/benefit ratio related to the installation of Toilé in a hospital setting. Both documents were set considering the results of the literature review and the economic evaluation obtained in this feasibility study.

Background

Introduction

The health emergency linked to SARS-CoV-2 infection and its potential transmission through contaminated surfaces in healthcare environments, has led to a more scrupulous attention to the problem of care-related infections (HCAI), both of viral and bacterial origin. In particular, the pandemic context has improved the necessity to carry out studies to evaluate the effectiveness of conventional disinfection methods to compare compared with alternative tools to prevent the spread of pathogens.

One of the main modes to transmit infections is by air. In hospital and healthcare settings, ventilation is the main control strategy for infectious diseases; it promotes air dilution resulting in the removal of respiratory viruses. (Francisco, 2014)

In an optimally ventilated environment, the number of droplets could be halved after 30 seconds, whereas in rooms with poor ventilation or no ventilation this could take 1-4 min and 5 min, respectively. (Somsen, 2020)

In toilets, air diffusion of potentially pathogenic microorganisms in faecal material during toilet flushing requires regular and good cleaning (e.g., ventilation + sterilization). In general, inadequate sewers and drainage systems (drains) increase the risk of contaminated air and the spread of infected particles, which may, in turn, settle on surrounding surfaces or directly infect the toilet user. Therefore, disinfection processes should be carried out frequently, but, in some cases, may not be sufficient to prevent the transmission of infections.

As specified, toilet cleaning should be accompanied by environment ventilation. On this aspect, WHO is focusing its efforts to provide concrete recommendations on how improve indoor ventilation and limit the exposure of individuals to pathogens, such as Sars-CoV-2. There are two projects about: the first aims to create a physical model to guide decision makers in developing ventilation standards in public environments. The second project is a tool available to all which calculate the risk of infection in closed environments based on parameters such as room size, the number of people, the existing ventilation or the size of the windows. (Fontana, 2022).

Healthcare-associated infections (HCAI): outlines of epidemiology and causes

Infectious risk, i.e. the risk for patients, visitors and caregivers to become infected during their stay in hospital or assisted living facilities, is one of the main management issues in healthcare settings.

Intentional evidence suggests that any infection that arises after at least 48 hours of hospitalization should be considered as associated with health care. (WHO, 2021)

Prerequisite is that the infection is not present, either in overt clinical form or incubating, at the time of hospital admission. Similarly, all infections that are not clinically manifest at the time of discharge but present at the patient's home, within a variable period ranging from 30 days (e.g., for surgical site infections) to 90 days after admission (e.g., joint implantation), are considered as a Healthcare-associated infections (HCAI). (Ricciardi, 2021)

HCAIs are infections caused by bacteria, viruses, or fungi, conventional or opportunistic pathogens, often multi-resistant. The main causes of HCAI in Europe are: Methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile and increasingly resistant Gram-negative bacteria. (ECDC, 2017)

As any other infection, the disease state depends on the encounter of three different orders of factors: factors associated with the individual, the microorganism, and elements associated with the environment. The latter consist of the surfaces (walls, beds, and objects) in the hospital and the people who come into contact with the patient, namely healthcare workers, family members, and visitors. (MdS, 2021)

Persons at risk for contracting an HCAIare primarily patients and, less frequently, hospital staff, volunteer caregivers, students, and interns. Conditions that increase susceptibility to infections include: age (infants, elderly), other infections or serious concomitant diseases (cancer, immunodeficiency, diabetes, anaemia, heart disease, renal failure), malnutrition, trauma, burns, altered consciousness, and organ transplants. (ISS, 2021)

In many European Union (EU) countries, HCAIs are periodically investigated with a point prevalence study using a standardized methodology proposed by the European Centre for Disease Prevention and Control (ECDC). These studies have shown that the prevalence of infected patients varies from 4.5%-6.7% (Table 2). On average, therefore, 5% of hospitalized patients become infected during hospitalization, whereas 7% to 9% of hospitalized patients are infected at any given time. However, these are average estimates, which therefore do not apply to specific contexts: the incidence of hospital infections. In fact, varies greatly depending on the size of the hospital, the type of ward, the length of stay and the control measures adopted. (ISS, 2021)

In Italy, there is no national surveillance system; however, several multicentre prevalence studies have been conducted (Table 1). By these indications and the literature, it can be estimated that in Italy 5-8% of hospitalized patients contract a hospital-acquired infection. (ISS, 2021)

Each year 450-700 thousand infections occur in hospitalized patients in Italy. It is estimated that about 30% are potentially preventable (135-210 thousand) and are directly the cause of death in 1% of cases (1350-2100 preventable deaths in one year). (ISS, 2021)

In 2016, in a sample of more than 14,000 inpatients in 19 Italian regions, 1,186 cases of HCAI were found, corresponding to 8% of the total number of inpatients. It shows a prevalence of HCAI, during the study, higher than the European average (6.5%). (HALT3, 2018) In addition, there is evidence of a wide variability in infection rates at regional level, determined by a number of factors and inhomogeneities in the application of policies to combat Antimicrobial Resistance (AMR), in the different level of antibiotic consumption and in the surveillance and monitoring systems of antibiotic-resistant infections. The regions with the highest rate of nosocomial infections are Lombardy and Lazio, respectively with 16.82% and 9.65% of hospitalized patients, the regions with lowest rate are Valle d'Aosta and Molise of 0.21% and 0.50% respectively. The Italian average, on the other hand, stands at 6.1%. (Ambrosetti, 2019)

According to the Ministry of Health, most HCAIs involve the urinary tract, the respiratory system, surgical wounds, and systemic infections (sepsis, bacteremia). The most frequent are urinary infections, which alone represent 35-40% of all hospital infections, while, following, respiratory infections represent 24%. The most frequently isolated microorganisms in HCAIs are gram-negative bacteria, including Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter species, with isolation rates of 24.17%, 58.66%, 12.66%, and 5.09%, respectively. (MoS, 2021)

Table 1 Multicenter studies of hospital infections conducted in Italy. (MoS, 2021)

Author, year	Location	Type of department and n° of hospitals or department	N° of patients	Frequency (%)
Zotti, 2000	Piemonte	Whole hospital (60)	9467	7.8
Di Pietrantoni, 2000	Italy	Whole hospital (10)	1315	9
Lizioli, 2000	Lombardia	Whole hospital (113)	18867	4.9
Nicastri, 2001	Italy	Whole hospital (15)	2165	7.5
Mongardi, 2001-2002	Emilia Romagna	Rsa (15), CP (34)	1926	9.6
Studio Spin, 2004	Veneto	Whole hospital (21)	6352	6.9
Ippolito, 2002	Italy	Whole hospital (32)	3306	6.9
Ippolito, 2003	Italy	Whole hospital (40)	3402	6.2
Ippolito, 2004	Italy	Whole hospital (48)	3416	5.4
Ippolito, 2004	Italy	Whole hospital (44)	2901	6.7
Rodelia, 2004	Italy	Whole hospital (41)	6631	4.5

Table 2 Estimated prevalence of healthcare-associated infections in European acute care hospitals, 28 EU/EEA countries

Country	Unitary sample	Patients with at least one HCAI in the sample (HCAI prevalence)		
	N	**n**	**%**	**95% CI**
Czech Republic	13,461	541	4.0	3.4–4.7
Belgium	11,8	856	7.3	6.4–8.3
Bulgaria	2,2	76	3.5	1.7–6.
Croatia	10,466	551	5.3	4.5–6.2
Cyprus	1,036	85	8.2	5.4–12.4
Czech Republic	15,117	1,015	6.7	5.9–7.6
Estonia	4,22	178	4.2	2.4–7.3
Finland	9,079	803	8.8	7.5–10.4
France	16,522	965	5.8	4.9–7.0
Germany	11,324	409	3.6	2.8–4.7
Greece	9,401	938	10.0	8.5–11.6
Hungary	20,588	818	4.0	3.3–4.8
Iceland	633	40	6.3	0.8–36.8
Ireland	10,333	633	6.1	5.0–7.5
Italy	14,773	1,186	8.0	6.8–9.5
Latvia	3,807	140	3.7	2.6–5.2
Lithuania	12,415	359	2.9	2.1–4.0
Luxembourg	2,018	103	5.1	4.0–6.5
Malta	961	60	6.2	5.2–7.4
Netherlands	4,441	170	3.8	3.4–4.3
Norway	9,628	495	5.1	4.1–6.4
Poland	21,712	1,249	5.8	4.8–6.9
Portugal	16,982	1,544	9.1	8.1–10.2
Romania	11,443	417	3.6	2.8–4.7
Slovakia	9,145	370	4.1	3.1–5.3
Slovenia	5,72	373	6.5	5.8–7.3
Spain	19,546	1,516	7.8	7.1–8.5
United Kingdom	20,148	1,297	6.4	5.4–7.6
England	3,813	234	6.1	4.8–7.9
United Kingdom	11,623	504	4.3	3.5–5.3
Northern Ireland	6,4	362	5.7	4.7–6.7
United Kingdom	**310,755**	**18,287**	**5.5**	**4.5–6.7**

The causes attributable to HCAI are multiple and can be summarized in the following points [www.salute.gov.it]:
- progressive introduction of new health technologies, with the prolonged use of invasive medical devices and complex surgical interventions, which, while improving therapeutic possibilities and the outcome of the disease, may favour the entry of microorganisms into normally sterile body sites;
- weakening of the body's defence system (immunosuppression) or serious concomitant diseases;
- poor application of environmental hygiene and infection prevention and control measures in the care setting;
- emergence of antibiotic-resistant bacterial strains, mainly due to the incorrect or excessive use of these drugs, which further complicates the course of many HCAIs.

Healthcare-associated infections (HCAI): modes of transmission and types of infections

The population with the higher risk to contract an HCAI are caregivers; however, healthcare workers and visitors are also exposed and can be affected.

The source of infection can be represented by a patient (colonized or with HCAI in place) or by the environment, meaning by environment the set of environmental matrices contaminated or improperly sanitized and by water, gas and ventilation systems not properly managed.

The modes of transmission of HCAIss can be summarized as follows: (MoS, 2021)

- Healthy vs sick contact;
- Indirect contact transmission by a contaminated vehicle;
- Transmission by direct or indirect contact with contaminated surfaces;
- Airborne transmission.

In all cases, in order to prevent transmission of infections, it is essential to:

- Identify the sources and microbiological agents responsible for the onset of infectious disease,
- quantify the potential impact on the health of healthcare personnel and users, due to exposure to single agents or mixtures thereof,
- identify appropriate technical remedies and environmental remediation solutions.

With regard to airborne transmission, it should be specified that organic particles suspended in the air (bioairs) and consisting of microorganisms (viruses, bacteria such as Legionella pneumophila, Staphylococcus aureus, Streptococcus pyogenes or Pseudomonas aeruginosa, yeasts, fungi such as Aspergillus fumigatus, Cladosporium spp. etc..) can spread and distribute even at great distances in all hospital environments, especially if carried by air conditioning systems not properly maintained.

In conclusion, the presence of a primary source of infection in care depends on: (ASR Emilia Romagna Region, 2006)

- health status of the subject exposed to crowded environments
- contact time or care time (duration of health procedures with direct patient/staff interaction)
- behavior (movements, ability to speak or cough-sneeze)

- degree of cleanliness of clothing;
- level of personal hygiene;
- staff training.

Approximately 80% of all hospital infections involve four main sites: the urinary tract, surgical wounds, the respiratory system, and systemic infections (sepsis, bacteremia). The most common are urinary infections, which alone account for 35-40% of all hospital infections. However, the last 15 years have seen a decline in these types of infections (along with surgical wound infections) and an increase in bacteraemia and pneumonia. The increase in systemic infections is a consequence of a gradual increase in specific risk factors, particularly the abundant use of antibiotics and vascular catheterizations. (ASR Regione Emilia Romagna, 2006)

With regard to the microorganisms involved, there have been changes in the agents responsible over time. Until the early 1980s, hospital infections were mainly due to gram-negative bacteria (e.g., Escherichia coli and Klebsiella pneumoniae). Then, as a result of antibiotic pressure and increased use of plastic medical supplies, infections sustained by gram-positive bacteria increased infections sustained by gram-positives (especially Enterococci and Staphylococcus epidermidis) and those by fungi (especially Candida), while those sustained by gram-negatives have decreased. (ISS, 2021)

Healthcare-associated infections (HCAIs): Clinical and Economic Impact

HCAIs have significant clinical and economic impacts. According to the World Health Organization's first global report, HCAIs result in longer lengths of stay, long-term disability, increased resistance of microorganisms to antibiotics, additional economic burden on health care systems and patients and their families, and significant excess mortality. (WHO, 2011)

In Europe, HCAIs cause annually:

- 16 million additional inpatient days;
- 37,000 attributable deaths;
- 110,000 deaths for which infection is a contributing cause. (WHO, 2011)

Based on data from the HCAI surveillance network, in Europe more than 3.2 million patients are infected at least once a year as a result of exposure to pathogens or opportunists in healthcare facilities. Also at the European level, as previously reported for Italy, the most common types of infections are urinary tract infections, pneumonia, surgical site infections, bloodstream infections and gastro-intestinal infections.

The European Centre for Disease Prevention and Control (ECDC) estimates that 3.8 million new cases of HCA and 90,000 deaths occur annually in intensive care hospitals in the countries of the European Union. The frequency and type of HCAIs vary from country to country but also from facility to facility. (ECDC, 2017)

Not all HCAIs are preventable: is currently estimated that more than 50% may be. Therefore, it is essential to selectively monitor those that are attributable to problems in the quality of care, intervene early, and adopt an organic and structured approach involving all professionals in care pathway. In general, infections associated with certain procedures can be prevented by reducing unnecessary procedures, choosing safer equipment, and adopting patient care measures that ensure aseptic conditions. (ISS, 2021)

HCAIs come at a cost in both health and economic terms to both the patient and the facility. Hence the need to adopt safe care practices that can prevent or control the transmission of infections both in the hospital and in all non-hospital healthcare facilities. Therefore, with a view to preventing the spread of viruses and bacteria through toilets, Planus SpA has created a toilet capable to aspire the emissions directly from the use of the toilet bowl, conveying it outside the building through the sewer duct. The medical device is part of a context of work safety (e.g, health workers) , and of contrast to resistant bacteria. In fact, its operation prevents the spread of microorganisms in the air after the completion of physiological functions of patients and consequently its adoption could reduce the high impact of nosocomial infections.

Technical Features

Toilé medical device

Due to the SARS-CoV-2 pandemic emergency, the attention of researchers has been focused, in the last year, on the transmission of viruses, bacteria and pathogens through air, including public toilets as a place of transmission.

The critical phase of a possible spread is represented by the flushing phase of the toilet. In fact, a strong turbulence is generated inside the toilet and the flow causes the expulsion of aery particles containing viruses and pathogens into the air. The consequence is the contagious of the surfaces and the surrounding environment. It is clear that hypothetical precautionary measures, such as the total exchange of air and the complete cleaning of the entire bathroom environment after each use, do not constitute a viable solution and would still be insufficient.

Toilé is part of an occupational safety context, in relation to the risk of contagion for healthcare workers, who are particularly exposed as they may be in contact with patients during the performance of their physiological functions and in any case operate in the toilets, or use them, in a high-risk environment such as healthcare facilities.

Toliè technology is a toilet capable to aspire air directly from the toilet bowl during use, conveying it outside the building through the sewer pipe. By sucking in the air at its source, the toilet thus created combats both the spread of unpleasant odours and that of viruses and other pathogens. The ceramics of Toilé are made in such a way as to have a dedicated duct for the suction of the contaminated air directly from the basin of the toilet. An aspirator built into the toilet is connected to this duct and directs the contaminated air directly into the sewer drain. (Planus, 2021)

In addition:

- -the separate chambers avoid overlapping flushing and aspirated air flows;
- the system continues its extraction activity throughout the time the toilet is in use especially, therefore, during the flushing phase;
- the aeraulic system (extraction and discharge of air containing contaminated air) is already inside the sanitary fixture and therefore does not require additional masonry work for the creation of dedicated piping;
- it has the hydraulic connections of any standard WC, according to the technical standard EN33, thus allowing a quick replacement with any WC.

Technology	Toilé
Producer company	Planus SPA
Class of risk	I
CE mark	YES
FDA Approval 510(k) Premarket Notification	NO
Technology life cycle phase	Pre-marketing

Technological Alternatives

Possible technological alternatives that could be adopted in public restrooms such as (i) traditional wall-mounted air extractors; or (ii) Air extractors connected to the flushing cistern. In the first case, the air exchange takes a long time and therefore it is not possible to prevent the diffusion of the air that will be inhaled by the next user and will settle on the surfaces, contaminating them. The use of the bathroom, in this case, should be compulsorily interdicted, until the process of total exchange is completed. In the second case, the suction takes place through the pipe that connects the flushing cistern to the toilet. However, with this system it is not possible to aspire the air because during the flushing phase the air suction capacity vanishes completely as such the pipe is full of water and it is not be able to aspire the air.

Figure 1 shows a Comparison Table of possible benefits between Toilé technology and possible technological alternatives, provided by the Company.

Figure 1 Comparison of the possible benefits of alternative technologies and Toilé technology (Source, Planus SPA)

Product	Extraction of contaminated air	Active during the flushing phase	Patented system and medical device	Reduce surface contamination	No added masonry works
Toilè	Yes	Yes	Yes	Yes	Yes
Wall drain extractors	No	No	No	No	No
Extractors connected to the waste tank	No	No	No	No	No

Setting of use

Toilé is part of a hospital prevention context and its adoption could reduce the high impact of nosocomial infections on patients' health, health workers' safety and, consequently, affect health system costs. The technology could be adopted in all public places where air purification of pathogens must be ensured such as public offices and schools, restaurants, etc.

Materials and Methods

Systematic Literature Review

The research question was explicated using the PICO model that includes the study population (P), the intervention evaluated (I), the comparator (C), and the outcomes of interest (O), as reported in Table 3.

Table 3 PICO model

Population	Population potentially affected by infections transmissible by the oro-fecal route
Intervention	Toilé WC
Comparator	Customary sanitary facilities, not equipped with an integrated suction system (setting: health care facilities)
Outcome	Prevention of air transmission of pathogenic microorganisms

The Pubmed and Web of Science databases were consulted for the literature review as of April 23, 2021. Table 4 below shows the strings used to search the individual databases. In addition to the Pubmed search, a manual search was also performed to gather additional evidence (Guidelines). In addition, some information concerning mainly the technical aspects of the technology was provided by the manufacturing company. The search string was differentiated according to the search engine consulted, to collect as much evidence as possible, consistent with the study.

Table 4 Search strings

Database	Research strings
Medline	((airs[MeSH Terms] OR airs/suspensions [All Fields] OR bioair [All Fields] OR air [All Fields]) AND (contamination [All Fields] OR "infection risk"[All Fields] OR dissemination [All Fields])) AND ("bathroom equipment" [MeSH Terms] OR toilet [All Fields] OR "toilet flushing"[All Fields] OR "toilet bowl surface"[All Fields]) AND hospitals[MeSH Terms]
Web of Science	((airs OR airs/suspensions OR bioair OR air) AND (contamination OR "infection risk" OR dissemination)) AND ("bathroom equipment" OR toilet OR "toilet flushing" OR "toilet bowl surface") AND hospitals

As for filters, the availability of English literature, studies conducted on humans and the possibility of consulting the abstract were considered. No time limits were set in order not to preclude ex ante the analysis of useful works, relevant to the topic under analysis. The research was completed through techniques of snow-ball analysis with the aim of expanding the number of studies and collect additional evidence.

Inclusion/exclusion criteria

The studies analysed by systematic literature review were considered eligible unless they met one or more of the following exclusion criteria:

- No relevance to the technology being evaluated;
- No relevance with the condition being evaluated;
- Unavailability of English or Italian versions of the study;
- Type of study not relevant (editorial, case report);
- Insufficient information on any of the aspects under evaluation;
- Duplicates of studies already found in the first database analysed.

The studies were classified using an Excel® spreadsheet containing an identification code for each study to indicate its source. In case of duplicate, the excel would indicate the first author, the year of publication, the title, the reference and the link to the abstract. The name of the first reviewer, the reasons for exclusion and useful notes for research purposes were also reported.

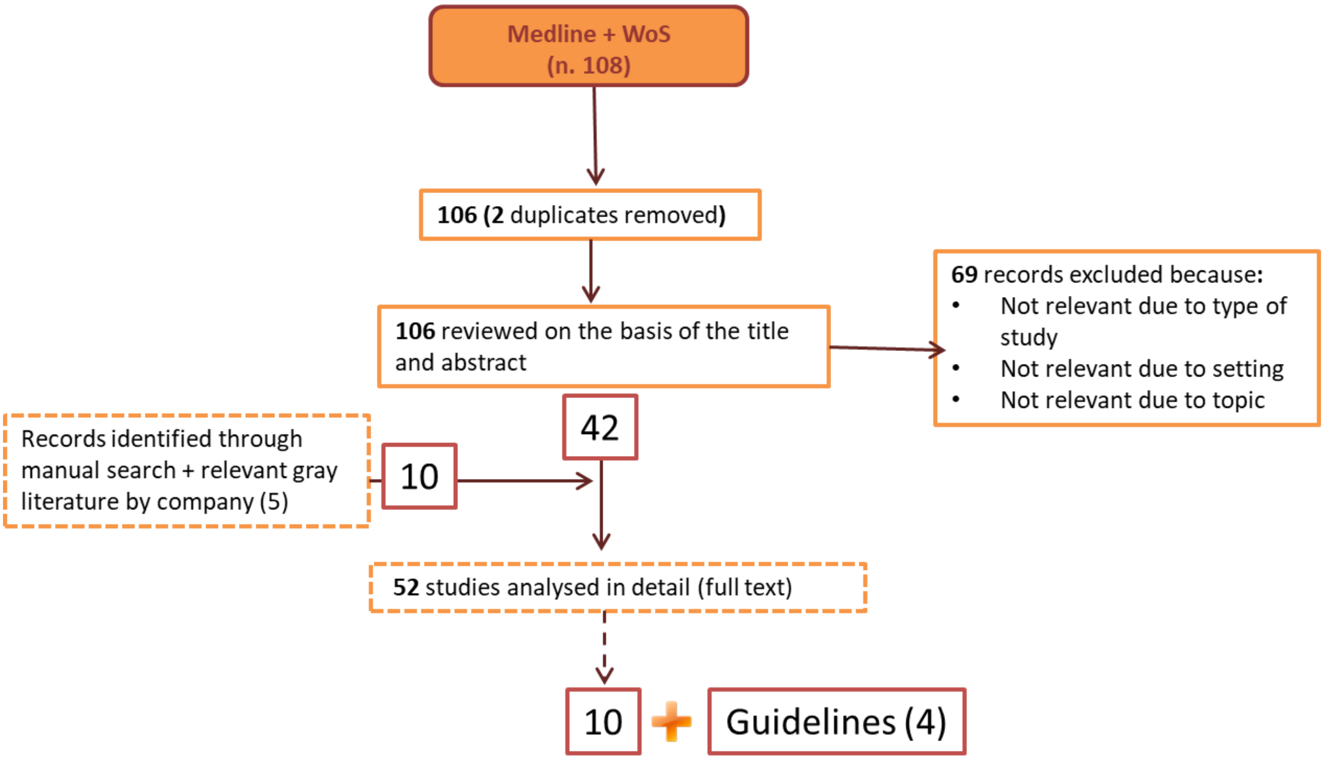
The first screening, based essentially on the title and the abstract, was followed by a second evaluation of the full text conducted by two junior researchers (FO, MDP) in double-blind. Any conflicts were resolved by two senior researchers (AF, EGC).

Results of the search strategy

The search strategy produced a total of 108 results. There were eliminated 2 duplicates and analysed106 records based on the title and abstract. From the first evaluation, 69 records were excluded basically for the following reasons: reference to a different technology and/or condition, or to another setting (e.g., home, rather than hospital), non-availability of English/Italian language. An additional 5 records were identified through a manual search, and 5 papers were shared by Planus Spa.

The candidate articles for the second screening were 52. After a full-test analysis, 10 studies were selected. The study selection process is illustrated in Figure 2 below.

Figure 2 PRISMA model. The diagram represents the literature review phase.



At the same time, it was conducted a manual search of the main guidelines useful for further framing of the subject under analysis.

Results of the Literature Review

Guidelines

The best-known definition of guidelines is the one formulated by the Institute of Medicine in 1992, which defines them as "recommendations developed in a systematic way to assist physicians and patients in making decisions about the appropriate management of specific clinical conditions." They are developed by a systematic review of the literature and expert opinions aiming to maximizing health care results and resources, but also to homogenize clinical practice in the presence of similar situations and to counteract the use of procedures with undocumented efficacy.

Guidelines are produced by multidisciplinary groups and offer a broad definition of good professional practice, being based on analysis, evaluation and systematic interpretation of scientific evidence.

The aim of the guidelines is to provide guidance to health professionals and users on the most appropriate choice of care in specific clinical situations, while ensuring clarity of pathways and responsibilities.

The Guidelines included in Toilé WC device feasibility study are as follows:

- Air conditioning systems: health and safety in inspection and remediation activities [INAIL, 2017] (https://www.inail.it/cs/internet/docs/alg-pubbl-impianti-climatizzazione.pdf).
- Guideline on the evaluation of the environmental sanitation process in hospitals and territorial structures for the control of healthcare-related infections (HCAI) [Associazione Nazionale dei Medici delle Direzioni Ospedaliere, 2018]; (https://www.anmdo.org/wp-content/uploads/2019/01/libro-uno-finzi-1.pdf).
- Guidelines for the prevention and control of enterobacteria, Acinetobacter baumannii and Pseudomonas aeruginosa resistant to carbapenems in healthcare settings [Ministero della Salute, 2020]; (https://www.salute.gov.it/imgs/C_17_pubblicazioni_2989_allegato.pdf).
- Information on ventilation / air conditioning systems in non-health community facilities and in domestic environments in relation to the spread of the SARS-CoV-2 virus [Rapporto ISS COVID-19 - n. 33/2020] (https://www.iss.it/rapporti-covid-19/ /asset_publisher/btw1J82wtYzH/content/rapporto-iss-covid-19-n.-33-2020-indicazioni-sugli-impianti-di-ventilazione-climatizzazione-in-strutture-comunitarie-non-sanitarie-e-in-ambienti-domestici-in-relazione-alla-diffusione-del-virus-sars-cov-2.-versione-del-25-maggio-2020)

1. AIR CONDITIONING SYSTEMS: HEALTH AND SAFETY IN INSPECTION AND CLEANING ACTIVITIES; INAIL, 2017

This guideline provides useful indications to promote the prevention of accidents and occupational diseases correlated to the inspection and/or cleaning activities of air conditioning systems; it also intends to contribute to the reduction of occupational risks through the promotion of safe behaviours and the correct use of equipment and collective and individual protection devices, which are fundamental for the protection of the health and safety of workers. In order to allow the association of the risks to the specific operating phase, the study provides an outline description of the different phases that characterize the interventions of control and restoration of aeraulic systems. It does not provide an indication of operating procedures for cleaning and sanitizing systems; for any further information on the various methods of intervention, please refer to the dedicated documentation.

2. GUIDELINE ON THE EVALUATION OF THE ENVIRONMENTAL SANITIZATION PROCESS IN HOSPITAL AND TERRITORIAL FACILITIES FOR THE CONTROL OF HEALTHCARE-RELATED INFECTIONS (HCAI); National Association of Hospital Management Physicians, 2018

This guideline contains indications and recommendations regarding the relationship between environmental hygiene and the risk of care-related infections and intends to suggest criteria for the evaluation and validation of the sanitization of care environments. Both hospital and territorial, considering the management and containment of clinical risk related to processes of environmental microbial contamination, proposing ways to control the process, result and outcome.

In particular, the document refers to the evaluation of innovative techniques and approaches, the definition of risk-related patient pathways and the measurement of the effectiveness of the production process, the microbiological result and the final outcome, i.e. the reduction of care-related infections through specific indicators.

The process indicators must be used to govern and therefore keep under control the salient phases of service delivery in the various risk areas, allowing timely intervention in case of non-compliance and are:

- Control of materials used,
- Control of operator activities
- Control of paper documentation,
- Control of machinery.

The Microbiological Result Indicators are used to understand the extent of microbial contamination present in the air and on the surfaces of the sanitized premises and to foresee corrective actions in case of exceeding the set standards.

Only those indications supported by scientific evidence have been included, considering also prescriptions provided by technical standards and mandatory legal requirements.

3. GUIDELINES FOR THE PREVENTION AND CONTROL OF ENTEROBACTERS, ACINETOBACTER BAUMANNII AND PSEUDOMONAS AERUGINOSA RESISTANT TO CARBAPENEMS IN HEALTHCARE FACILITIES; Ministry of Health, 2020

The primary objective of this guideline is to provide recommendations on early recognition and specific CPI practices and procedures necessary to effectively prevent the emergence and to control the spread of carbapenemase-resistant Enterobacteriaceae (CRE) - carbapenemase-resistant Acinetobacter baumannii (CRAB) - carbapenemase-resistant Pseudomonas aeruginosa (CRPsA) colonization and infection in acute care facilities. They are also intended to provide an evidence-based framework to inform regarding the development and/or strengthening of national and facility IPC policies and programs to control transmission of CRE-CRAB-CRPsA in different types of health care facilities. Recommendations may be tailored to the local context based on information collected prior to implementation and, therefore, influenced by available resources and public health needs. The guidelines for CRE-CRAB-CRPsA build on the foundation provided by the 2016 WHO Guidelines on the Core Components of a National and Acute Health Facility Infection Prevention and Control Program (40), with the aim of detailing best practices and procedures to prevent and control the spread of CRE-CRAB-CRPsA in health care facilities. The Guideline Development Group (GDG) assessed the importance of these components, along with evidence from the systematic reviews, and developed the recommendations listed in this document, designed to align with and reinforce the core principles of IPC. It is important to note that the numbered list of IPC recommendations included in these guidelines is not intended as an order of importance of each component. Furthermore, not all recommendations are relevant to our study.

The recommendations, proposed in this LG, are as follows:

- Recommendation 1: implementation of multimodal infection prevention and control strategies;
- Recommendation 2: importance of hand hygiene compliance for the control of CRE-CRAB-CRPsA;
- Recommendation 3: surveillance of CRE-CRAB-CRPsA infection and surveillance cultures for asymptomatic CRE colonization;
- Recommendation 4: contact precautions;
- Recommendation 5: patient isolation;
- Recommendation 6: cleanliness of the environment;
- Recommendation 7: Surveillance cultures for environmental colonization/contamination by CRE-CRAB-CRPsA;
- Recommendation 8: monitoring, auditing, and feedback.

In particular, Recommendation 6, or "cleanliness of the environment," advocates cleanliness (and maintenance of the built environment) as a key element in preventing HCAIs and pathogen cross-transmission.

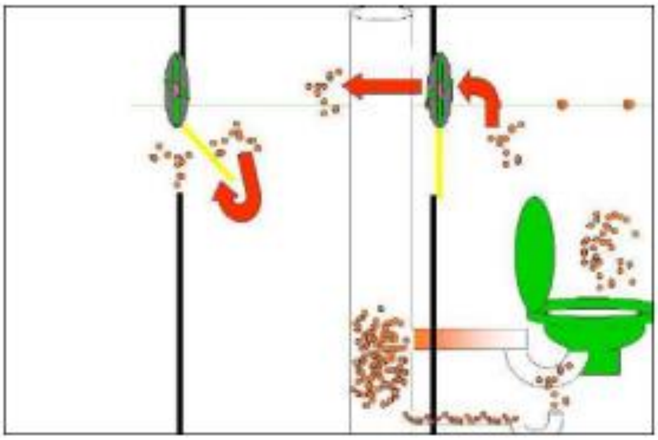
The workgroup recommends that, compliance with environmental cleanliness protocols be always ensured in the areas immediately surrounding patients colonized or infected with CRE-CRABCRPsA (the "patient zone").
Tis guidlineworkgroup , considered that most cleaning products, including hypochlorite, are usually reasonably priced. The workgroup noted that some cleaning agents (e.g., hydrogen peroxide), despite being obviously effective, can impede workflow in the hospital. It was noted that while some studies cited the effective use of hypochlorite, it could be associated with occupational health problems if not used according to proper instructions.
In addition, according to the definition included in the WHO Guidelines on Hand Hygiene in Health Care "patient area" includes the patient and the areas immediately surrounding the patient. Usually this includes all inanimate surfaces that are touched by or in direct physical contact with the patient, such as bed rails. It also includes surfaces frequently touched by caregivers during care, such as monitors, doorknobs, and buttons, and other "high frequency" touch surfaces. Contamination is also likely in bathrooms and associated items.
The optimal cleaning product of environmental hygiene protocols for areas immediately surrounding patients colonized or infected with CRE-CRAB-CRPsA has yet to be defined. Three studies of CRE-CRAB-CRPsA used hypochlorite (generally at concentrations of 1000 parts per million, ppm) as the agent to accomplish environmental cleaning.
It was considered essential the use of multimodal strategies to implement environmental clean-up. These include institutional policies, structured training, and monitoring compliance with cleaning protocols.

4. INDICATIONS ON VENTILATION/CLIMATIZATION SYSTEMS IN NON-HEALTHY COMMUNITY STRUCTURES AND HOME ENVIRONMENTS IN RELATION TO THE DIFFUSION OF THE SARS-COV-2 VIRUS; Report ISS COVID-19 - n. 33/2020

Indoor air quality and microclimate, also modulated by outdoor seasonal conditions, may represent key factors in infection transmission and seasonal epidemiological patterns in indoor environments. Adequate ventilation and regular air exchange in this type of environment, as well as to maintain conditions of comfort, are necessary to ensure the healthiness by reducing the concentration of particulate matter and pollutants of biological nature. Therefore, conditions favouring the ventilation of indoor environments become of priority importance and, where it is not possible or sufficient to make use of natural ventilation, it is necessary to install forced ventilation devices that require appropriate maintenance, especially if they are in environments where there is an increased risk of spreading diseases.
The adaptation to contingent conditions, during the so-called phase two of the emergency which was preceded by a long lockdown period, has significated a "new social perception of indoor environments" cannot be ignored and must find an appropriate response in measures to contain the risk of transmission of the SARS-CoV-2 virus with appropriate prevention and protection procedures.
In this context, the document has described the main components of ventilation and air conditioning systems that can facilitate the movement of air in indoor environments within non-

healthcare community facilities and home environments and has also provided operational recommendations for the management of these systems.
Particular attention should be paid, however, based on the experience of the SARS-COV epidemic, to eliminating conditions that may lead to shunts or short circuits of air between the external air intake (supplying the environment) and the external exhaust duct of air taken from indoor environments in centralized systems. In particular, avoiding that the air inlet and exhaust air inlets are close together, at a short distance from each other and opposite each other, or avoiding that the air recovery systems from non-ventilated rooms (e.g. bathrooms, warehouses, etc.) are placed in series and verifying that the exhaust air inlets are far from the inlet and ventilation air inlets (Figure 3).

Figure 3 Modes of remote transmission of viruses from airs of oro-fecal derivation through aspiration systems



Ventilation can result in the movement of air masses from one room to another adjacent room, with transport of any suspended bioair. In fact, the outgoing air flow rate from an environment is equal to the incoming air flow rate. In addition to controlled mechanical ventilation systems of all kinds, there will be infiltration in and out through the building envelope, both with the outside and with adjacent environments.
The air movement depends on the difference between the pressures at the two sides of each partition, which, in general, also depends on the specific climatic conditions (wind direction and intensity, temperature difference and chimney effect of the buildings) as well as on the active aeraulic systems.
On the other hand, the ventilation system, if the recovery of air does not take place in the same environment of input, in a balanced way, can lead to the spread of pathogens to adjacent environments.
Therefore, the management of the air conditioning and ventilation system must be adapted to the characteristics of the system and the way in which the rooms are used.

Summary of clinical studies

At the end of the process of study selection, 10 articles were selected and then systematized in a summary table to facilitate analysis. As previously mentioned, the spread of enteric viruses and bacteria can occur via air and droplets produced by flushing, leading to potential contamination of the surrounding environment. In the study by Best E.L. et al (2012), the objective was to demonstrate the likelihood of the risk of aerial dissemination of C. *difficil*e by airproduced as a result of flushing a toilet. The authors performed in situ tests, using faecal suspensions of C. *difficile* to simulate the bacterial load found during the symptomatic phase of illness, and then to measure the presence of C. *difficile* in the air released during flushing of two different types of toilets commonly used in hospitals. Specifically, the authors concluded that toilets without lids, as is often the case within public health facilities, can spread contaminated particles into the environment. High percentages of C. *difficile* were detected in the air sample recovered immediately after flushing, but contamination of surrounding surfaces was also observed, demonstrating the release of relatively large droplets capable of contaminating the environment surrounding the toilet.

Verani M. et al (2014) estimated the risk of exposure and infection by environmental air monitoring and sampling of surfaces from 3 hospital bathrooms before and after routine cleaning operations. Overall, viruses were detected in 78% on surfaces and 81% on the air. Compared with Best et al, the effectiveness of routinely used decontamination methods was also evaluated in the study by Verani et al. Cleaning, understood as disinfection, did not seem to reduce contamination substantially, leading the authors to conclude that toilets represent an important source of contamination, especially within healthcare settings, where disinfection has shown a crucial role in preventing the spread of pathogens, although proving to be potentially ineffective or insufficient in some cases.

The choice of the detergent may also play a crucial role in preventing the contamination of toilet surfaces observed following flushing. Sassi H.P. and colleagues, in 2017 specifically investigated the effectiveness of decontaminating toilet surfaces following the use of common disinfectants such as bleach, hydrogen peroxide, quaternary ammonium, and peracetic acid. These chemical agents would appear to be useful in reducing the pathogen load on the most at-risk surfaces, as ascertained by sampling performed in the pre/post toilet flush study. Significant differences were observed based on the disinfectant agent used and the contact time of the reagent with the contaminated surface (1 - 15 - 30 minutes). Of all the disinfectants tested, peracetic acid and quaternary ammonium showed the greatest reduction for the 1-minute contact time.

Table 5 Literature review data extraction summary table.

Author	Year	Microorganisms	Population		Sanitizing system	
			Healthcare workers	Patients	surfaces (disinfectants)	air (aeration)
Best E.L.	2012	*C. difficile*		X		
Abreu A.C.T.	2013	*Nosocomial pathogens*			X (chlorine and aldehydes)	
Matoušková I.H.	2014	*Legionella pneumophila, Micrococcus spp., Bacillus spp, Staphylococcus aureus, Enterobacter, E. coli, Klebsiella spp,*		X	X (not specified)	X
Verani M.	2014	*Norovirus, Enterovirus, Rhinovirus,* Human *rotavirus,* and *Torque teno virus*			X (not specified)	
Cooper J.B.	2016			X		X
Sassi H.P.	2017	Ebola virus (EBV)		X	X (bleach, hydrogen peroxide, quaternary ammonium and peracetic acid)	
Knowlton S.D.B.	2018			X		
Wilson G.M.	2020	*Clostridioides difficile, Enterococcus faecalis, Enterococcus faecium*		X		

Chia P.Y.S.	2020	*CR Enterobacteriaceae (CRE), CR A. baumanii (CRAB), CR P. aeruginosa (CRPA), and other Multidrug-resistant Gram-negative organisms (MDRGN)*		X		
Alsved M.F.	2020	*Airborne Norovirus*		X		X
Constantinides B.	2020	*Escherichia coli, Klebsiella pneumoniae and Klebsiella oxytoca*		X		
Per Vink J.	2020	*Enterobacteriaceae Extended Spectrum Beta-Lactamase (ESBL)* *Multi-Drug Resistant Gram Negative Bacilli (MDR-GNB).*		X	x (not specified)	
Tran H.N.	2020	SARS-COV 2				
Couturier J.	2020	*Legionella pneumophila*		X		X
Reigadas E.	2020	*Clostridium difficile*	X	X	X	
Sevin T.	2020	*Enterobacteriaceae Extended Spectrum Beta-Lactamase (ESBL)*	X	X	X	
Abney S.E.	2021	Faecal bacteria *and Salmonella*		X	X (sodium hypochlorite)	
Lou M.	2021	Bacteria and virus		X		
Jolivet S.	2021	Gram negative carbapenemi resistent organism		X		

The massive use of disinfectants has as a drawback the increase in the occurrence and wide spread of multi-resistant microbiological forms. In such a scenario, in which few compounds are able to inhibit or kill infectious agents, maintaining a hospital environment in acceptable hygienic conditions requires the implementation of appropriate strategies. Abreu A.C.T. et al (2013) performed a systematic review to examine several new disinfection alternatives. including that with water vapor, which demonstrated a reduction in Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE) and P. aeruginosa (to undetectable values) within 5 s of the application of a vapor system. Gas-plasma is another promising alternative for sterilization. The latter can be applied in various healthcare settings, although it is primarily aimed at equipment rather than surfaces. Plasma, on the other hand, consists of a mixture of photons, electrons, ions, atoms, and radicals (such as atomic oxygen atomic oxygen, ozone, nitrogen oxides).

In addition, the study provides up-to-date information on conventional (e.g., alcohol) and emerging and alternative (e.g., UV light) disinfection strategies, which are especially promising for hospital environments.

Alcohol-based disinfectants cause protein denaturation and are effective against vegetative bacterial forms, fungi, and viruses, but have no effect on spores. Concentrations of residual chlorine can be quite effective in removing biofilms from surfaces, requiring short exposure times for growth inhibition. However, these chemicals are corrosive to metals and can be inactivated by the presence of organic matter. In addition, in recent years the use of chlorine has been associated with the formation of carcinogenic compounds, and some pathogens have been shown to be resistant to chlorine. Aldehyde-based disinfectants have antimicrobial activity against spores, bacteria, viruses and fungi.

UV rays, on the other hand, are effective in eliminating C. *difficile* spores, which are usually difficult to inactivate. In any case, the efficacy of the different disinfection methods varies according to the adhesion strategy of the pathogen to the surface and the characteristics of the surface itself. Different biofilm removal strategies should be selected according to the context and may require the use of different removal media that act synergistically to increase their effectiveness. However, it is also important to always consider the risk of evolution of resistant strains when developing new disinfection procedures.

Cooper J.B. et al (2016) also evaluated the effectiveness of an irradiation device (ultraviolet C - 254-nm system; ASEPT.1X; Sanuvox, Saint-Laurent, QC, Canada) by comparing samples taken from surfaces of a restroom in which the automated system had been installed versus a restroom without such a mechanism. The 5-minute ultraviolet decontamination cycle started automatically upon failure to detect movement by infrared sensors (the cycle stopped automatically if a new user entered the restroom). Air samples were collected using a SAS 360 dual-headed bioair sampler (Bioscience International, Rockville, MD) from the two types of toilets 5 minutes and 30 seconds after each use, timing to account for decontamination cycles. From the colony counts grown on the plates used (Oxoid, Nepean, ON, Canada), the authors concluded that the installed UVC beams can be a useful supplementary decontamination tool in hospital public restrooms shared by many patients. The epidemiological study by Matoušková I.H. and colleagues (2014) showed that the measures to prevent fungal infections taken at the Transplant Unit-Hemato-Oncology Clinic (University Hospital Olomouc) are effective. These consist in:

- HYD HKBCA 0150 air-conditioner (Nickel Prague, Prague, Czech Republic), which has 3 separate filtration systems for cooling, heating, humidification;
- Aqua Osmotic Tišnov (Aqua Osmotic Systems, Tišnov, Czech Republic) for water filtration (potability);
- Drinking water is pre-treated using the Aqua Osmotic 100K UV light system and reverse osmosis. Boilers heat water to temperatures above 64 °C (Legionella prevention);
- In isolation box toilets, the end of the shower hose and faucet are equipped with an end filter (Ionpure-Siemens, Hoffman Estates, IL, USA) with a filter membrane, pore size 0.22 µm (to prevent water with Legionella from escaping).

Annual monitoring revealed no risks above the acceptable threshold with respect to transmission of infections either by airs or through contaminated surfaces.

More recently, particulate matter and bioair concentrations were measured by Knowlton S.D.B. et al in 2018 (22) in hospital bathrooms under three sampling conditions:

- NO fecal waste / NO discharge,
- NO fecal waste / Yes discharge,
- YES fecal waste / YES discharge.

Air sampling was performed with a specific sampler both before and after flushing at distances of 0.15, 0.5, and 1 min from the toilet for 5, 10, 15 min. Microbial concentrations were significantly higher in toilets following flush use, yet no difference in bioair concentration was revealed over time and distance, supporting the most accepted hypothesis that bioairs are generated by toilet flushing and can cause surface contamination and exposure to increased risk of inhalation of contaminated material among both patients and healthcare workers.

Similarly, Wilson G.M. et al (2020) evaluated surface contamination and toilet bioair in the bathrooms of patients admitted with C. difficile infection. Room air was collected continuously for 20 minutes with a bioair sampler before and after flushing (toilets had no lids). A total of 72 pre-flush and 72 post-flush samples were collected; 9 of the pre-flush samples (13%) and 19 of the post-flush samples (26%) were culture positive for healthcare-associated bacteria. The predominant species detected were Enterococcus faecalis, E. faecium, and C. difficile. Compared to the pre-flush samples, the post-flush samples showed significant increases in concentrations, again demonstrating that bioairs produced by toilet flushing potentially contribute to hospital environmental contamination.

In addition, the results of Alsved M.F. et al (2020) suggest that air may be the main source of dissemination of Norovirus, the main cause of viral gastroenteritis. In more detail, air samples were taken in the room of patients with gastroenteritis, in the corridor near the door, and in the bathroom directly connected to the patient's room. The authors found the presence of Norovirus RNA in sub-micrometer particles concluding that airborne transmission may be an important route of infection.

Chia P.Y.S. t al (2020) performed a review of the literature, including evidence produced from 2014 to 2019, especially delving into the topic of Gram-negative organisms expressing an higher resistance. This review emphasizes the importance of prevention especially in hospital settings as places most involved in the transmission of infections. Given the variability of the various studies reviewed, the authors also affirm the need to promote further investigations that take into account the climate of the various countries, the type of patients considered, the presence of ventilation mechanisms within the departments examined, and the possibility of importing prevention guidelines in low-middle income countries. Clustering in this sense may provide further enlightenment on the most appropriate prevention methods based on the factors mentioned above.

Focus on the risk for health workers related to the presence of bioairs in hospital toilets

From the discussion with the experts involved in the Advisory Board of this project has emerged the need to address the risk to health workers related to the presence of bioairs in hospital toilets. It was, therefore, conducted a narrative review of the literature of the most recent scientific articles published in the last two years on the subject to be investigated.

Healthcare workers are involved in the transmission of infectious diseases related to the presence of bioareosols in the toilets present in the care setting, either because they are directly exposed to orofecal bioair, and not only from toilets, or because they themselves are vectors of bioair deposited on their hands and resulting from the emptying, for example, of urine containers in toilets. (Reigadas, 2020; Goldstein, 2020)

According to the study of Constantinides B. at al (2020) the drains of hospital sinks are extensively contaminated by species belonging to the family of Enterobacteriaceae causing, therefore, healthcare-associated infections, In addition, they may represent potential reservoirs of antibiotic-resistant microorganisms. Populations of antibiotic-resistant E. coli and Klebsiella spp. can also be persistent colonizers of sinks. Thus, the association between contaminated and unremediated wastewater reservoirs (including sink drains) in healthcare settings with outbreaks of colonization/disease with antibiotic-resistant Gram-negative bacilli is quite clear.

Per Vink J. et al (2020) performed a systematic review of the literature on the nosocomial acquisition of extended-spectrum beta-lactamase-producing Entebacteriaceae (ESBLs) and Multidrug-resistant Gram-negative bacteria (MDR-GNBs). This study shows that the highest infection rates in Europe were found among carbapenemase-resistant organisms and carbapenemase-producing Klebsiella pneumoniae (KPC). This suggests that, although ESBLs have spread widely and are well described in the literature, the focus of Infection Prevention and Control (IPC) measures within hospitals should be better directed toward organisms that have higher infection rates. The meta-analyses performed in this review analyzed studies in which patients were isolated in single rooms versus non-isolated, finding no significant difference in prevalence or rates of infection during hospitalization between these two subgroups.

Tran H.N. et al (2020), on the other hand, performed a systematic review of the literature, stating that to date, although the existence of SARS-CoV-2 coronavirus in untreated wastewater is confirmed, evidence on the survival time of the virus in aquatic environments is lacking. The most common route of transmission of SARS-CoV-2 in water, sewage, and wastewater is through the feces of symptomatic persons. Current disinfection methods used in the drinking water treatment process appear to effectively inactivate SARS-CoV-2 in water.

Couturier J. et al (2020), in a French study, described two cases of healthcare-associated legionellosis in patients admitted 5 months apart to the same room. The infection was probably caused by Legionella pneumophila transmitted through contaminated toilet water that airized during flushing. The other commonly suspected sources, in this case the shower and sink, tested negative for L. pneumophila.

Reigadas E. et al (2020) evaluated the extent of Clostridium difficile contamination in both the environment and healthcare workers. They performed environmental sampling at the bed rails, toilet, bathroom faucet, door handle, alcohol-based dispenser, and call bell. In contrast, for health care workers, hand swabs were performed (on a voluntary basis) at the same time as environmental sampling. The authors state that they found significant contamination on both the hands of the workers and the sampled surfaces and that even after isolation measures were performed, the contamination on the surfaces was still significant.

Another research, Sevin et al (2020) demonstrated that contamination in urine by Enterobacteriaceae producing broad-spectrum beta-lactamases can be a source of cross-transmission with environmental contamination. In fact, the authors evaluated the level of contamination after emptying toilet containers and subsequent rinsing in the sink and, showed that if it contains resistant enterobacteria, environmental contamination can be spread. Therefore, when using reusable urine containers, it is important to remind caregivers to empty and wash them at the disposals in order to limit environmental contamination. It should be noted that the area with the highest risk of colonization was found to be the bottom of the toilet bowl, the sink and the faucet. With regard to healthcare workers, professional clothing was rarely found to be contaminated, with the exception of gloves.

According to Abney S.E. et al (2021) sodium hypochlorite cleaners are effective in reducing fecal bacteria levels on toilet surfaces. Exposure to pathogens can occur due to failure to clean and disinfect areas within a restroom, as well as poor hand hygiene. The use of automatic toilet cleaners can reduce the number of microorganisms expelled during flushing. For example, Salmonella can colonize the underside of the rim of toilets and persist for up to 50 days. In addition, pathogenic enteric bacteria appear in greater numbers in the biofilm of toilets than in the water. Lou M. et al (2021), on the other hand, examined bioairs generated by toilets and wastewater treatment sections, modes of bioair generation, and other factors involved in health risk assessment.

It was showed that toilet bioairs are significantly affected by toilet types and flushing energy. The most effective strategy to prevent the transmission of germs, microorganisms, and viruses is to reduce the production of germs or viruses in the toilet. In addition, moving air can dilute bioair concentrations, so decrease bioair concentrations as much as possible by intensifying the ventilation device.

Finally, Jolivet S. et al. (2021) showed that drains, sinks, and faucets are the sites most frequently contaminated with Pseudomonas aeruginosa. In addition, when flushed, toilets gush producing airs. Airization of microorganisms from contaminated toilets during flushing has been repeatedly demonstrated for various types of toilets. In these cases, transmission of microorganisms is attributed to the water jet directly onto the patient or to contamination of the environment. In addition, the authors describe a high prevalence of carbapenemase-producing bacteria in sink drains, especially near toilets, suggesting sink contamination through droplets produced during toilet flushing.

Economic Evaluation

Introduction

Numerous official studies carried out at international level have shown that bacteria and viruses, including Coronavirus, are widely present in faeces and consequently in the air generated during flushing. Studies conducted in this context have shown that the air released from the toilet remains in suspension in the air of the bathroom environment for several hours, becoming a source of diffusion, including viruses such as SARS-CoV-2, which can be inhaled by a health worker or a subsequent user. The use of the toilet also generates bacteria and viruses in the form of air that is deposited on all surrounding surfaces, increasing the risk of infection. Planus SpA has designed a toilet that is able to suck air directly from the basin of the toilet during use, conveying it outside the building through the sewer pipe. By sucking up the air at its origin, the toilet thus created counteracts both the spread of bad odors and that of viruses and other pathogens. This new medical device is part of a context of safety at work, with regard to the risk of contagion for health workers, who are particularly exposed as they may be in contact with patients during the performance of their physiological functions and in any case operate in toilets, or use them, in a high-risk environment such as health facilities.

This analysis aims to carry out a feasibility study to investigate the clinical and organizational characteristics related to the use of the Toilet Toilet device. In this feasibility study, the use of the new device will be evaluated in order to define the strengths and weaknesses related to its adoption in a hospital setting. In addition, a budget impact model will be developed in order to estimate the economic impact of an eventual implementation in a hospital setting.

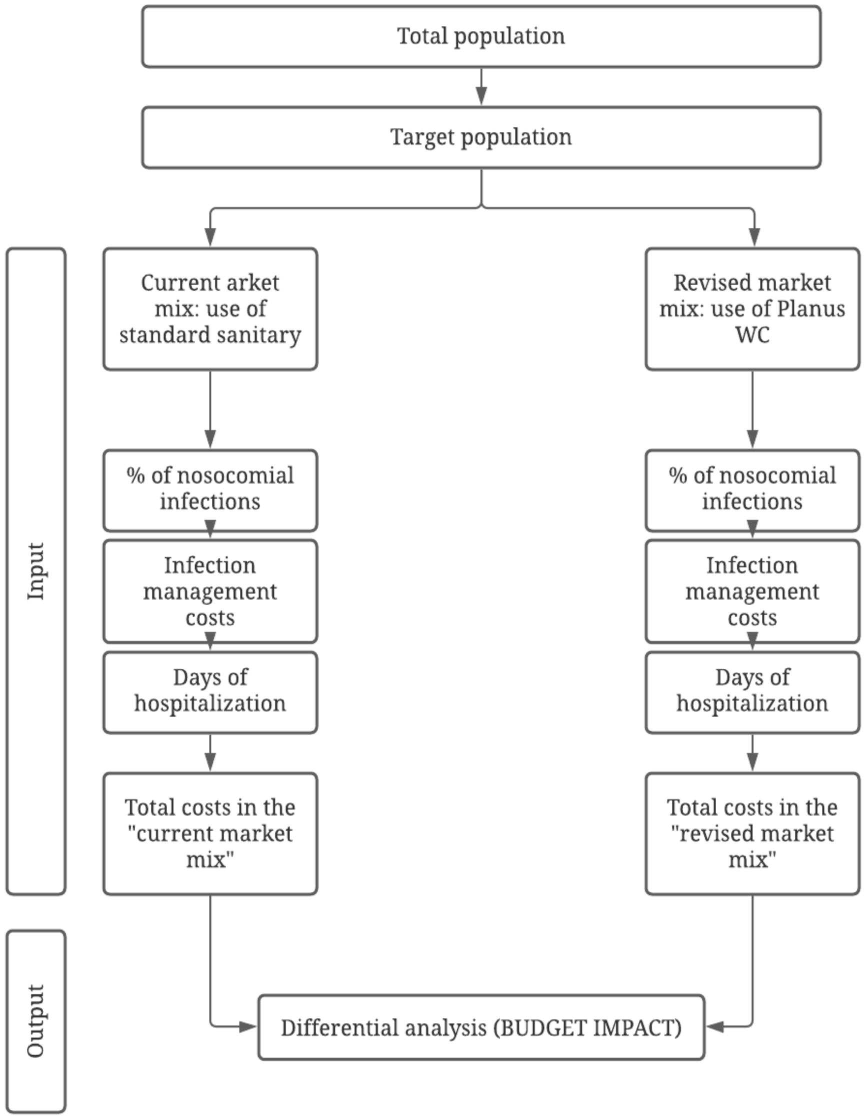
Methods

A budget impact analysis (BIA) is an economic evaluation that estimates the financial consequences of adopting a new intervention. The BIA assesses whether the intervention is cost-effective from a financial point of view. In this analysis, the unit cost of an intervention is taken into account by multiplying it by the number of potential users to evaluate the total budget required to finance the introduction of the new technology. Therefore, starting from the size of the population identified, a budget impact analysis is developed through the structuring of four decision trees, or one per pathogen, for each year under analysis. This model allows to evaluate the effectiveness of the treatment sequencing used in the specific tree and to estimate the total costs and the number of infections contracted from the current use of the Standard of Care (SoC) in the Italian hospital setting and in the case of the introduction of Toilé technology.

In particular, in the present analysis, two alternative scenarios were considered:

- a current scenario (AS IS) that does not consider recourse to the Toilé alternative;
- an alternative scenario (TO BE) in which increasing annual recourse rates to Toilé are assumed over the time horizon considered, equal to three years.

Figure 4 shows the economic evaluation scheme conducted in the analysis of this study.



Target Population

The model initially considers the population of hospitalized patients in Italy of 8,193,592 (PDF data 2019). Starting from this figure and dividing it over the percentage of hospitalized patients with nosocomial infections, namely 6.10% (Nicastri et al., 2003), it was possible to extrapolate the number of patients who develop nosocomial infections, which is 499,809. The most contracted bacteria at the nosocomial level are Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter species, with 293,211, 120,781, 60,390, and 25,427 patients, respectively, being part of the aforementioned cohort (AR-ISS 2019 Report data). These patients were considered as the reference population within the budget impact model.

Market Share

Market shares were developed through data provided by the company Planus SpA distinct for the two scenarios under analysis: the first correspond0nding to the current market mix (AS IS), i.e., the scenario in which the entire eligible population uses only the SoC of available hospital-based healthcare; the second based on the revised market mix (TO BE), in which the inclusion of Toilé in the market is assumed and a 3% annual increase in device use, resulting in a decrease in the rate of comparator use (Table 6).

Table 6 Rate of use of therapeutic alternatives - AS IS scenario vs TO BE scenario

SCENARIO AS IS	Year 1	Year 2	Year 3
Toilé	0 %	0 %	0 %
Other treatment	100 %	100 %	100 %
SCENARIO TO BE	**Year 1**	**Year 2**	**Year 3**
Toilé	3 %	6 %	9 %
Other Treatment	97 %	94 %	91 %

Economic valorization of the treatment strategies

In order to evaluate the economic value of the strategies under analysis, first of all a therapeutic sequencing based on three lines of antibiotic antagonists was drawn up for each of the four pathogens examined, both for the AS IS Scenario and for the TO BE Scenario in order to determine the economic burden for the National Health System associated with the treatment of these patients considering the potential development of resistance to some antibiotics. Treatment strategies were defined as best supportive care for each bacterium with the support of clinicians with proven experience in the Italian care setting in the management of nosocomial infections. The therapeutic sequencing identified for the two scenarios are reported in Table 7.

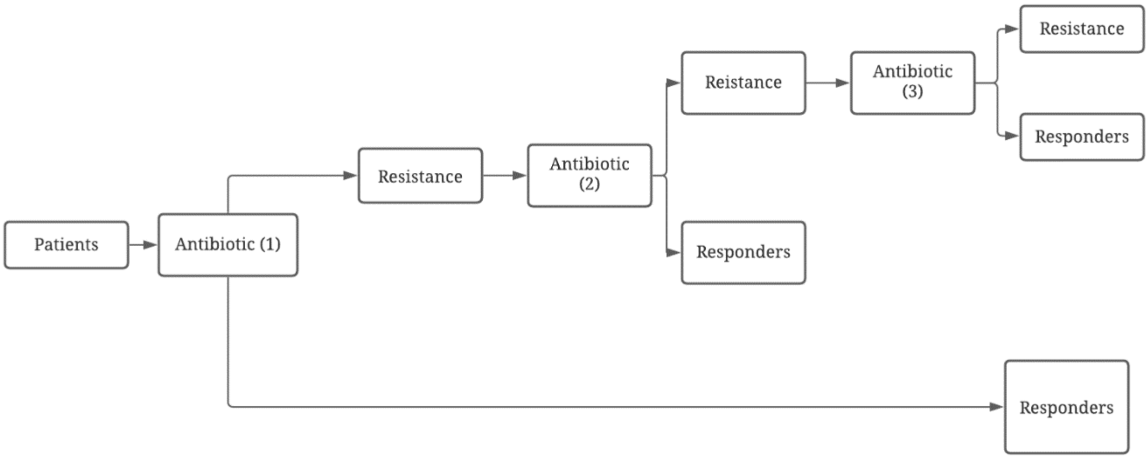
Table 7 Therapeutic sequencing in the two scenarios under analysis

ESCHERICHIA COLI	First line	Second line	Third line
Strategy 1 (scenario AS IS)	Ceftriaxone	Meropenem	Amoxicillina-Acido Clavulanico
Strategy 2 (scenario TO BE)	Ceftriaxone	Meropenem	Amoxicillina-Acido Clavulanico
KLEBSIELLA PNEUMONIAE	**First line**	**Second line**	**Third line**
Strategy 1 (scenario AS IS)	Amoxicillina-Acido Clavulanico	Amoxicillina-Acido Clavulanico	Amoxicillina-Acido Clavulanico
Strategy 2 (scenario TO BE)	Amoxicillina-Acido Clavulanico	Amoxicillina-Acido Clavulanico	Amoxicillina-Acido Clavulanico
PSEUDOMONAS AERUGINOSA	**First line**	**Second line**	**Third line**
Strategy 1 (scenario AS IS)	Piperacillina – Tazobactam	Cefepime	Levofloxacina
Strategy 2 (scenario TO BE)	Piperacillina – Tazobactam	Cefepime	Levofloxacina
ACINETOBACTER SPECIES	**First line**	**Second line**	**Third line**
Strategy 1 (scenario AS IS)	Ciprofloxacina	Ciprofloxacina	Ciprofloxacina
Strategy 2 (scenario TO BE)	Ciprofloxacina	Ciprofloxacina	Ciprofloxacina

The analysis was based by the creation of a decision tree structured to identify, for each therapeutic line and bacterium considered, the number of patients responding to the specific drug sequencing as well as the number of resistant patients so as to estimate the total cost of sequencing for each pathogen. Model development was supported by data available in the 2019 AR-ISS Report from which resistance values for each class of antibiotic to the four gram-negative bacteria considered were extrapolated. These resistance rates were multiplied by the population developing nosocomial infections on each arm of the strategy to determine the number of responding patients. For each line of treatment, several parameters useful for estimation were identified:

- the population remaining from the previous line;
- the quality of life resulting from the health condition (data extrapolated from the studies of Ernst et al., Brasel et al., Beusterien et al. and YORK CHE);
- the costs associated with treatment, which are composed of:
    - cost of antibiotic therapy, derived from the product of the number of patients in the line in question, the daily cost of the antibiotic (source obtained from the transparency list of class H drugs), and the length of stay, expressed in days, which varies depending on whether the patient is responding or not
    - Cost of hospital stay, calculated through the ratio of population, length of stay (again depending on whether the patient is compliant or not), and the weighted average cost of the stay ("Green Paper on Public Expenditure" 2015 and Tan et Al. "Direct cost analysis of intensive care unit stays in four European countries: applying a standardized costing methodology")

Figure 5 Structure of the decision tree made for estimating outcomes



Results

Table 8 reports the results of the analysis expressed as the total cost of the two scenarios considered and as a differential analysis between the costs incurred for the share of nosocomial infections related to the use of sanitaryware and the acquisition costs of the device considering the potential reduction in nosocomial infections that Toilé is able to bring. To characterize the uncertainty of the parameters considered in the model, a deterministic sensitivity analysis was implemented to estimate the impact of different scenarios on the results of the model. The results show that, in the AS IS Scenario, the number of infections and the annual costs arising from the pharmacological treatment of patients determine an economic burden for the NHS of €14,280,625,377.76 over the time horizon considered.

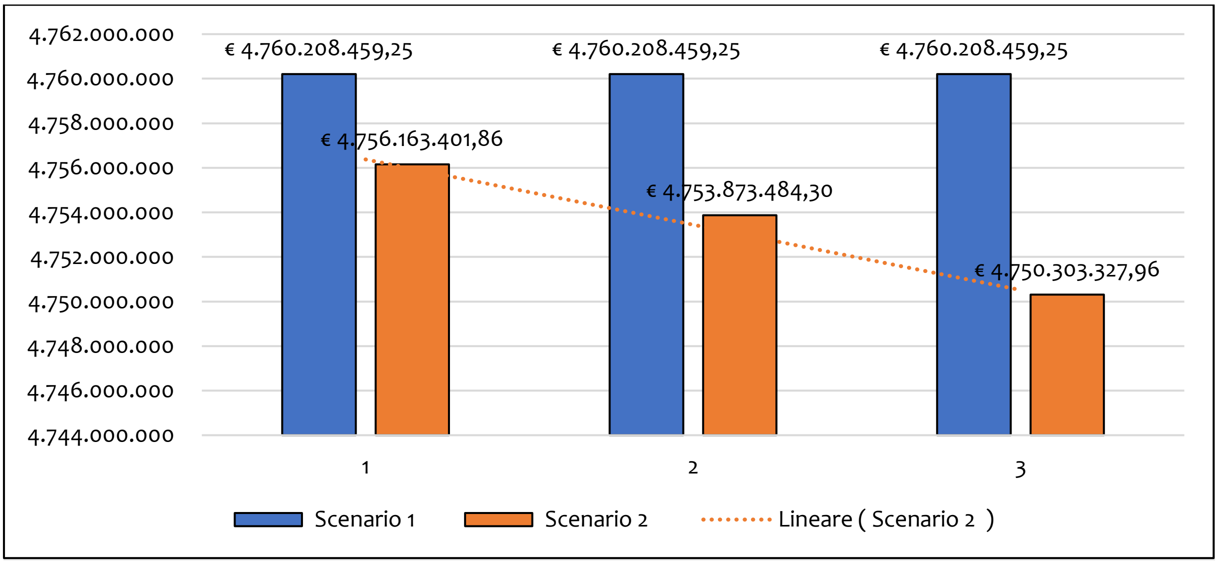
Table 8 Resource absorption in AS IS and TO BE scenario by cost driver and year of analysis

SCENARIO CURRENT MARKET MIX (WITHOUT TOILÉ)				
	Year 1	Year 2	Year 3	Total
Acquisition costs	-	-	-	
Installation costs	-	-	-	
Number of infections	499.809	499.809	499.809	
Total cost of antibiotic therapy	€ 4.689.261.098	€ 4.689.261.098	€ 4.689.261.098	€ 14.067.783.293,37
Total cost of hospital management	€ 70.947.361	€ 70.947.361	€ 70.947.361	€ 212.842.084,39
TOTAL	**€4.760.208.459**	**€4.760.208.459**	**€4.760.208.459**	**€14.280.625.377,76**
SCENARIO REVISED MARKET MIX (WITH TOILÉ)				
	Year 1	Year 2	Year 3	Total
Acquisition costs	€ 749.151 €	€ 749.151	€ 749.151	
Installation costs	€ 56.186 €	€ 56.186	€ 56.186	
Number of infections	499.434	499.059	498.685	
Total cost of antibiotic therapy	€ 4.684.463.913	€ 4.682.227.206	€ 4.678.710.260	€ 14.045.401.380
Total cost of hospital management	€ 70.894.151	€ 70.840.940	€ 70.787.730	€ 212.522.821,27
TOTAL	**€ 4.756.163.402**	**€4.753.873.484**	**€ 4.750.303.328**	**€ 14.260.340.214,12**
DIFFERENTIAL ANALYSIS				

	Year 1	Year 2	Year 3	
Acquisition costs	€ 749.151	€ 749.151	€ 749.151	
Installation costs	€ 56.186	€ 56.186	€ 56.186	
Number of infections	- 375	- 750	-€ 1.125	
Total cost of antibiotic therapy	-€ 4.797.185	-€ 7.033.892	-€ 10.550.837	
Total cost of hospital management	-€ 53.211	-€ 106.421	-€ 159.632	
TOTAL	**-€ 4.045.057**	**-€ 6.334.975**	**-€ 9.905.131**	**-€ 20.285.164**

In the TO BE Scenario, on the other hand, the expenditure borne by the NHS over the time horizon considered is equal to €14,260,340,214.12. It can be seen, therefore, that, in the face of an initial expense associated with the costs of acquiring and installing the Toilet device and the progressive increase over the three years of the percentage of use, there is a decrease in the number of patients who contract nosocomial infections and, consequently, a saving of resources resulting from the avoided costs associated with this decrease, both in terms of antibiotic therapy and hospital stay (Figure 4).

Figure 6 Comparison of total resource uptake in AS IS and TO BE scenarios by year of analysis

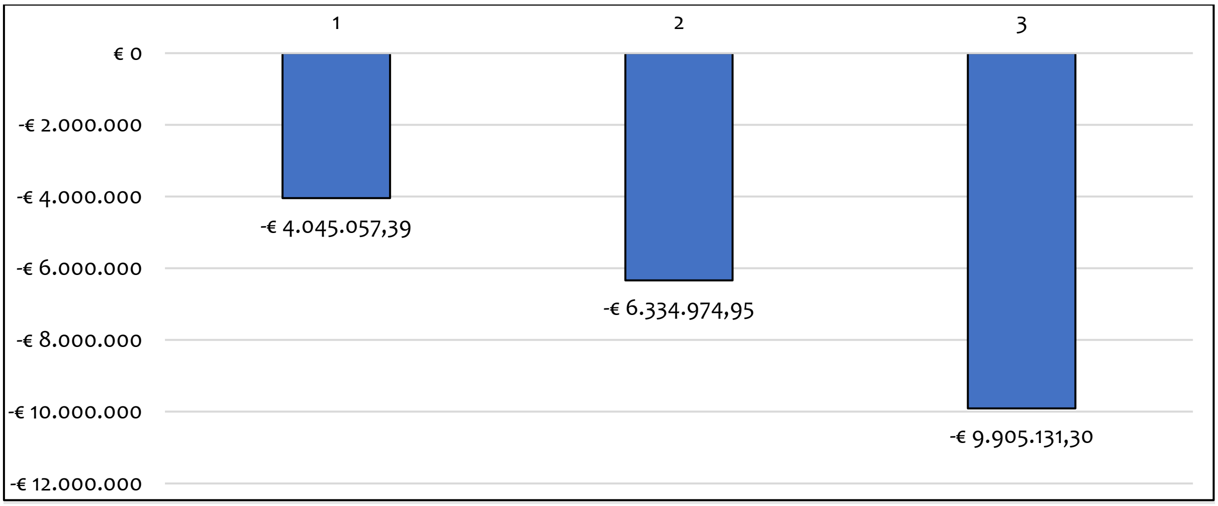


From the comparison between the two scenarios, it is possible to evaluate the economic effect on the National Health Service by considering the trend evolution expected for the market before and after the introduction of Toilé in hospital environments. The AS IS Scenario is associated with a higher absorption of resources in each year of analysis compared with the TO BE Scenario, thanks to the strong reduction in infections, with savings of €4,045,057 in the first year, €6,334,975 in the second year and €9,905,131 in the third year, respectively, and a total saving of €20,285,164 (Table 9).

Table 9 Comparison of total resource absorption - AS IS scenario vs TO BE scenario

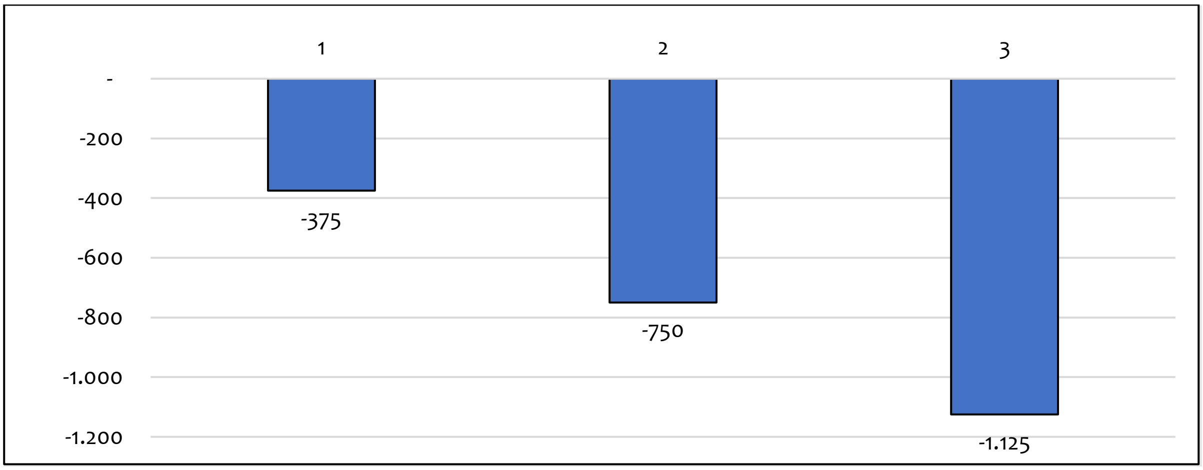
	Year 1	Year 2	Year 3
Scenario AS IS	4.760.208.459	4.760.208.459	4.760.208.459
Scenario TO BE	4.756.163.402	4.753.873.484	4.750.303.328
	Year 1	**Year 2**	**Year 3**
BI Total	-4.045.057	-6.334.975	-9.905.131
BI Cumulative Total	-4.045.057	-10.380.032	-20.285.164

Figure 7 Graphical representation by year of analysis budget impact total



The results show how the increase in market share associated with the introduction of Toilé and the economic relief for the National Health System are directly proportional. Each new device installed is equivalent to a saving in economic and organizational terms for the System. In addition, it is important to consider the decrease in the number of infections with a consequent, more cost-effective management of the occupation of hospital beds. In fact, in the time frame considered, Toilé makes it possible to reduce the number of infections contracted in the hospital setting by 7% every year, for a total of 2,249 infections avoided over 3 years. This would guarantee an additional 12,500 patients the use of inpatient beds and thus a more efficient turnover of the same.

Figure 8 The graph represents per year the analysis of the number of nosocomial infections prevented

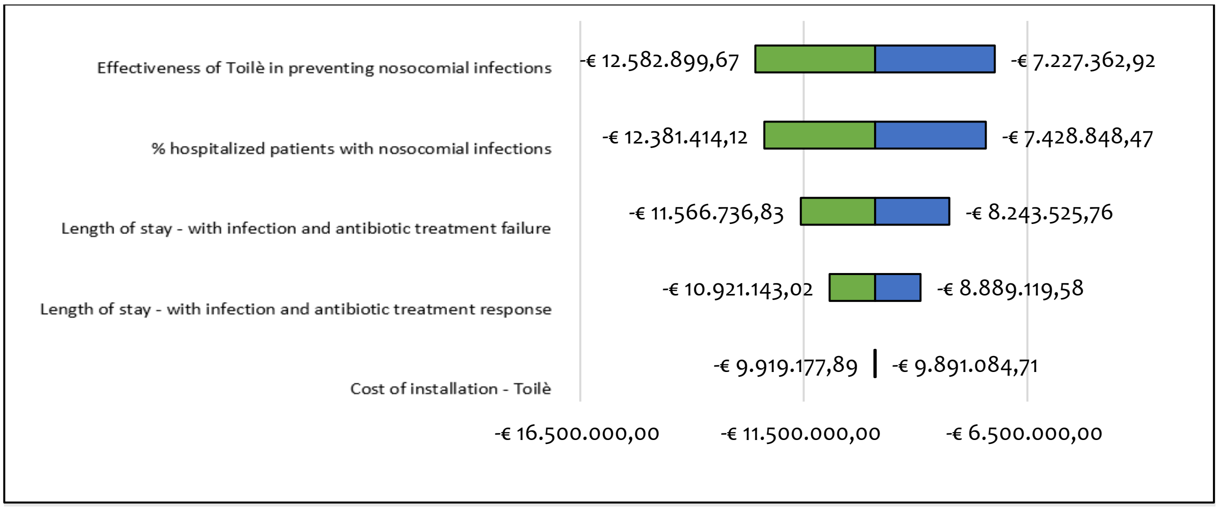


As far as the cost of annual use is concerned, a daily use of 5 hours was estimated (by excess), equal to 1,825 hours/year. By comparing these values with the KW/h absorption of Toilé, an annual usage cost of €30 was estimated, which, for reasons of simplicity of the analysis and considering the low incidence of this expense on the overall costs, was not considered in the analysis.

Sensitivity analysis

In order to characterize the uncertainty of the parameters used in the budget impact model, a deterministic sensitivity analysis was conducted using a tornado graph shown in graph 4. Specifically, the analysis investigates the impact of the results deriving from a deviation of some of the parameters considered in the analysis assuming a level of uncertainty equal to 25% of their average value.

Table 10 Univariate sensitivity analysis.



As can be seen from the results (Figure 7), the parameter that determines the greatest deviation from the results of the case-base is represented by the percentage of effectiveness of Toilé in preventing nosocomial infections. Among the other parameters characterized by greater uncertainty we find the percentage of patients hospitalized with nosocomial infections and the length of stay for patients with infection and failure to receive antibiotic treatment. The parameters, instead, characterized by a lower degree of uncertainty, that is, whose deviation has a marginal impact on the results of the analysis, are represented by the length of stay for patients with infection and response to antibiotic treatment and the cost of installation of Toilè.

Bibliography

Abreu, A. C., Tavares, R. R., Borges, A., Mergulhão, F., & Simões, M. (2013). Current and emergent strategies for disinfection of hospital environments. *Journal of Antimicrobial Chemotherapy*, 68(12), 2718-2732.

Alsved, M., Fraenkel, C. J., Bohgard, M., Widell, A., Söderlund-Strand, A., Lanbeck, P.,

ASR Regione Emilia Romagna. Dossier 123-2006 Epidemie di infezioni correlate all'assistenza sanitaria Sorveglia e Controllo

Associazione Nazionale dei Medici delle Direzioni Ospedaliere. Linea guida sulla valutazione del processo di sanificazione ambientale nelle strutture ospedaliere e territoriali per il controllo delle infezioni correlate all'assistenza (HCAI). 2018. Available online: (https://www.anmdo.org/wp-content/uploads/2019/01/libro-uno-finzi-1.pdf).

Best, E. L., Freeman, J., & Wilcox, M. H. (2012). Models for the study of Clostridium difficile infection. *Gut microbes*, *3*(2), 145-167.

Chia, P. Y., Sengupta, S., Kukreja, A., Ponnampalavanar, S. S., Ng, O. T., & Marimuthu, K. (2020). The role of hospital environment in transmissions of multidrug-resistant gram-negative organisms. *Antimicrobial Resistance & Infection Control*, 9(1), 1-11.

Ciobotaro P, Oved M, Nadir E, Bardenstein R, Zimhony O. An effective intervention to limit the spread of an epidemic carbapenem-resistant Klebsiella pneumoniae strain in an acute care setting: from theory to practice. Am J Infect Control. 2011;39(8):671-7.]

Constantinides B, Chau KK, Quan TP et al. Genomic surveillance of Escherichia coli and Klebsiella spp. in hospital sink drains and patients. Microb Genom. 2020 Jul;6(7):mgen000391. doi: 10.1099/mgen.0.000391. PMID: 32553019; PMCID: PMC7478627.

Cooper, J., Bryce, E., Astrakianakis, G., Stefanovic, A., & Bartlett, K. (2016). Efficacy of an automated ultraviolet C device in a shared hospital bathroom. *American journal of infection control*, 44(12), 1692-1694.

Decreto legislativo 507/93 "Attuazione della direttiva 90/385/CEE concernente il ravvicinamento delle legislazioni degli Stati membri relative ai dispositivi medici impiantabili attivi". Disponibile online. https://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=13207.

Directive 93/42/EEC "Medical devices". Disponibile on line https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices_en.

Direttiva 90/385/EEC "Active implantable medical devices". Disponibile online https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/implantable-medical-devices_en.

Dlgs 46/97 "Attuazione della direttiva 93/42/CEE concernente i dispositivi medici. Available online: https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=1997-03-06&atto.codiceRedazionale=097G0076&elenco30giorni=false. Last Access 6/07/2021

E Reigadas , S Vázquez-Cuesta , L Villar-Gómara , R Onori , L Alcalá , M Marín , P Muñoz , E Bouza. Role of Clostridioides difficile in hospital environment and healthcare workers.

ECDC. Economic evaluations of interventions to prevent healthcare-associated infections. 2017

Enfield KB, Huq NN, Gosseling MF, Low DJ, Hazen KC, Toney DM, et al. Control of simultaneous outbreaks of carbapenemase- producing Enterobacteriaceae and extensively drug-resistant Acinetobacter baumannii infection in an intensive care unit using interventions promoted in the Centers for Disease Controlcand Prevention 2012 carbapenemase-resistant Enterobacteriaceae toolkit. Infect Control Hospital Epidemiol. 2014;35(7):810-7]

Francisco, J. S., Hazra, M. K., & Sinha, A. (2014). Hydrolysis of glyoxal in water-restricted environments: formation of organic air precursors through formic acid catalysis. *The Journal of Physical Chemistry A*, *118*(23), 4095-4105.

Hand hygiene technical reference mannual. Geneva: World Health Organization; 2009 (http://www.who.int/infectionprevention/tools/handhygiene/evaluation_feedback/en)

INAIL. Impianti di climatizzazione: salute e sicurezza nelle attività di ispezione e bonifica. 2017. Disponibile on line: https://www.inail.it/cs/internet/docs/alg-pubbl-impianti-climatizzazione.pdf).

Istituto Superiore di Sanità-Epicentro. Infezioni correlate all'assistenza-Informazioni generali. Disponibile online: https://www.epicentro.iss.it/infezioni-correlate/.

Istituto Superiore di Sanità-Epicentro. Infezioni correlate all'assistenza-Aspetti epidemiologici. Disponibile online: https://www.epicentro.iss.it/infezioni-correlate/epidemiologia.

Jeanne Couturier, Christophe Ginevra, Didier Nesa, Marine Adam, Cyril Gouot, Ghislaine Descours, Christine Campèse, Giorgia Battipaglia, Eolia Brissot, Laetitia Beraud, Anne-Gaëlle Ranc, Sophie Jarraud, Frédéric Barbut. Transmission of Legionnaires' Disease through Toilet Flushing. Emerg Infect Dis 2020 Jul;26(7):1526-1528. doi: 10.3201/eid2607.190941.

Knowlton, S. D., Boles, C. L., Perencevich, E. N., Diekema, D. J., & Nonnenmann, M. W. (2018). Bioair concentrations generated from toilet flushing in a hospital-based patient care setting. *Antimicrobial Resistance & Infection Control*, *7*(1), 1-8.

Matoušková, I., & Holy, O. (2014). Monitoring of the environment at the transplant unit—hemato-oncology clinic. *International journal of environmental research and public health*, *11*(9), 9480-9490.

Mengmeng Lou, Shuai Liu, Chunjie Gu, Huimin Hu, Zhengkun Tang,Yaopeng Zhang, Chenye Xu & Fang Li Published: 24 October 2020. The bioairs emitted from toilet and wastewater treatment plant: a literature review. Environmental Science and Pollution Research volume 28, pages2509–2521 (2021)

Ministero della Salute. Infezioni correlate all'assistenza: cosa sono e cosa fare. www.salute.gov.it – ultimo accesso il 21.07.2021

Ministero della Salute. Linee guida per la prevenzione e il controllo di enterobatteri, *Acinetobacter baumannii* e *Pseudomonas aeruginosa* resistenti ai carbapenemi nelle strutture sanitarie. 2020. Available online: https://www.salute.gov.it/imgs/C_17_pubblicazioni_2989_allegato.pdf.

Ministero della Salute. Malattie infettive. Disponibile online: https://www.salute.gov.it/portale/malattieInfettive/dettaglioContenutiMalattieInfettive.jsp?lingua=italiano&id=648&area=Malattie%20infettive&menu=ica. Ultimo accesso: 22.07.2021

Rapporto ISS COVID-19 - n. 33/2020. Indicazioni sugli impianti di ventilazione/climatizzazione in strutture comunitarie non sanitarie e in ambienti domestici in relazione alla diffusione del virus SARS-CoV-2. 2020. Disponibile on line: (https://www.iss.it/rapporti-covid-19/ /asset_publisher/btw1J82wtYzH/content/rapporto-iss-covid-19-n.-33-2020-indicazioni-sugli-impianti-di-ventilazione-climatizzazione-in-strutture-comunitarie-non-sanitarie-e-in-ambienti-domestici-in-relazione-alla-diffusione-del-virus-sars-cov-2.-versione-del-25-maggio-2020.

Regolamento 2017/745 del Parlamento Europeo e del Consiglio. Available online: http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=4971&area=dispositivi-medici&menu=caratteristichegenerali.

Report italiano HALT3 2016/2017, studio di prevalenza europeo sulle infezioni correlate all'assistenza e sull'utilizzo di antibiotici nelle strutture di assistenza socio-sanitaria extraospedaliera, Università di Torino,2018

Report Italiano PPS2 2016/2017 – Studio di Prevalenza Italiano sulle Infezioni Correlate all'Assistenza e sull'uso di Antibiotici negli Ospedali per Acuti.

S.E. Abney,K.R. Bright,J. McKinney,M. Khalid Ijaz,C.P. Gerba. Toilet hygiene—review and research needs. S.E. Abney,K.R. Bright,J. McKinney,M. Khalid Ijaz,C.P. GerbaFirst published: 26 April 2021.

Sarah Jolivet, Jeanne Couturier , Xavier Vuillemin, Cyril Gouot, Didier Nesa, Marine Adam, Eolia Brissot, Mohamad Mohty, Rémy A Bonnin,Laurent Dortet,Frédéric Barbut. Outbreak of OXA-48-producing Enterobacterales in a haematological ward associated with an uncommon environmental reservoir, France, 2016 to 2019. 2021 May;26(21):2000118.doi: 10.2807/1560-7917.ES.2021.26.21.2000118.

Sassi, H. P., Reynolds, K. A., Pepper, I. L., & Gerba, C. P. (2018). Evaluation of hospital-grade disinfectants on viral deposition on surfaces after toilet flushing. *American journal of infection control*, *46*(5), 507-511.

Sattar SA, Maillard JY. The crucial role of wiping in decontamination of high-touch environmental surfaces: review of current status and directions for the future. Am J Infect Control. 2013;41:S97-S104

Somsen, G. A., van Rijn, C., Kooij, S., Bem, R. A., & Bonn, D. (2020). Small droplet airs in poorly ventilated spaces and SARS-CoV-2 transmission. *The Lancet Respiratory Medicine*, *8*(7), 658-659.

Suarez C, Pena C, Arch O, Dominguez MA, Tubau F, Juan C, et al. A large sustained endemic outbreak of multiresistant Pseudomonas aeruginosa: a new epidemiological scenario for nosocomial acquisition. BMC Infect Dis.2011;11:272.

T Sevin V Goldstein ,I Lolom , F Lenne , Y Gaudonnet , A L Baptiste , G Bendjelloul , L Armand-Lefevre, J C Lucet. Bathroom contamination by antibiotic-resistant Enterobacterales (ESBLPE and CPE): an experimental study. 2020 Oct;106(2):271-276.. Epub 2020 Aug 1.PMID: 32750383
The European House-Ambrosetti S.p.A. Curare è salute. 2019. Disponibile on line https://fondazionecerm.it/wp-content/uploads/2019/11/AMBROSETTI-Meridiano-Sanit%C3%A0-2019.pdf. Ultimo accesso 19.11.2021
Torsten Holmdahl, Christina Isaxon, Anders Gudmundsson, Patrik Medstrand, Blenda Böttiger & Löndahl, J. (2020). Sources of airborne norovirus in hospital outbreaks. *Clinical Infectious Diseases*, *70*(10), 2023-2028.
Tran HN, Le GT, Nguyen DT, Juang RS, Rinklebe J, Bhatnagar A, Lima EC, Iqbal HMN, Sarmah AK, Chao HP. SARS-CoV-2 coronavirus in water and wastewater: A critical review about presence and concern. Environ Res. 2021 Feb;193:110265. doi: 10.1016/j.envres.2020.110265. Epub 2020 Oct 1. PMID: 33011225; PMCID: PMC7528884.
UNI EN ISO 14155:2012. Indagini cliniche dei dispositivi medici condotte su soggetti umani - Buona pratica clinica.
Verani, M., Bigazzi, R., & Carducci, A. (2014). Viral contamination of air and surfaces through toilet use in health care and other settings. *American journal of infection control*, *42*(7), 758-762.
Vink J, Edgeworth J, Bailey SL. Acquisition of MDR-GNB in hospital settings: a systematic review and meta-analysis focusing on ESBL-E. J Hosp Infect. 2020 Nov;106(3):419-428
W.Ricciardi, S.Boccia. Igiene, Medicina Preventiva e Sanità Pubblica.III edizione 2021
WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level, 2016 https://www.who.int/gpsc/core-components.pdf)
WHO guidelines on hand hygiene in health care. Geneva: World Health Organization; 2009 (http://apps.who.int/iris/bitstream/10665/44102/1/9789241597906_eng.pdf)
WHO. Report on the Burden of Endemic Health Care-Associated Infection Worldwide. 2011. Available online: http://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf;jsessionid=9E17F1D48F1F12A50A7EB8910A701FC6?sequence=1
Wilson, G. M., Jackson, V. B., Boyken, L. D., Schweizer, M. L., Diekema, D. J., Petersen, C. A., Breheny P. J., Nonnenmann M.W., Perencevich E.N., & CDC Prevention Epicenter Program. (2020). Bioairs generated from toilet flushing in rooms of patients with Clostridioides difficile infection. *Infection Control & Hospital Epidemiology*, *41*(5), 517-521.
World Health Organization. Health Care-Associated Infections. Fact Sheet. Available online: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf Last Access: 22.07.2021

Sitography

www.salute.gov.it
https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf;jsessionid=980C06DBA96633BECBAA1568F15FF8B5?sequence=1
https://www.eunethta.eu/

corriere.it/salute/malattie_infettive/21_dicembre_25/covd-oms-ventilazione-361b2010-6409-11ec-b1af-a17af24cc52d.shtml