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Capital and operational expenditures of different operating room air-handling installations with conventional or ultra-clean air supply systems

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ABSTRACT

When making a decision on the operating room air handling installation and type of air supply system, it is relevant to know the expenditures of the different air handling installations and air supply systems. The aim of this study was to determine the capital and operational expenditures of air handling installations equipped with an ultra-clean or with a conventional system. To compare the technical requirements of Dutch air handling installations with European standards and guidelines, and evaluate the costs of surgical site infections in comparison with the capital expenditures. This study fills a gap in knowledge, detailed technical information and costs of air handling installations and air supply systems from multiple completed projects of 24 hospitals were collected, analyzed and compared. Per OR capital expenditures increase by €62,491 to €139,018 when an air handling installation with an ultra-clean system is compared to a conventional system, which is 3%–7% of the total construction costs of a completely new OR department. The yearly increase in operational expenditures per OR with an ultra-clean system compared to a conventional system was €673 to €1,896. The capital and operational expenditures of air handling installations with an ultra-clean system are higher than those with a conventional system. The technical specifications of the ORs studied in the Netherlands correspond to European standards and guidelines. When the impact on patient suffering and costs associated with surgical site infections are weighed against the investment required for an air handling installation with an ultra-clean system, it is worth considering.

1. Introduction

An air handling installation (AHI) in the operating room is used to create an overpressure and a comfortable and safe environment for the patient and surgical staff [1]. There are several ways to supply air to an operating room (OR). Operating room air handling installations with a conventional (CV) air supply system are mixing the supplied air evenly in the entire OR diluting the concentration of

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harmful substances. An air handling installation with an ultra-clean (UCV) air supply system distributes the introduced clean air towards the ultra-clean zone [2]. The ultra-clean zone is intended for positioning the wound area of the patient, sterile staff, and instrument tables during the surgical procedure [3–7].

New UCV systems such as temperature-controlled air-flow (TcAF) and controlled Dilution Ventilation (cDV) systems are introduced in the market and claim the whole OR to be ultra-clean during surgery. They provide a system suitable for all types of surgery (class 1a, 1b) [3–8]. The ultra-clean air quality standard for a UCV system in the ultra-clean zone, in terms of micro-organism counts, should not exceed 10 CFU/m^3 during surgery [3,4,6,8]. To meet these requirements higher air volumes are introduced in the OR [9–11]. The air supply volumes of UCV systems are higher (approximately 7,000–10,000 m^3/h) when compared to the air volumes of CV systems (approximately 2,000–3,000 m^3/h). When lower air volumes are used the number of micro-organisms in the whole OR will be higher, which is a risk factor for the incidence of Surgical Site Infections (SSI) [9,12,13]. With air volumes defined by standards and guidelines [4–7], it is not possible to achieve a protected area [5,6] or clean zone [4] as with a UCV system.

The World Health Organization (WHO) recommends an optimum of around 20 Air Changes per Hour (ACH) to dilute the micro-organisms generated in the OR [20]. The by WHO [14] advised 20 ACH is in most cases not sufficient to achieve the desired number of≤10 CFU/m^3 in the ultra-clean zone [3,4,9,13].

National standards and guidelines in Europe are advising the number of ACH [4,7] or a fixed introduced air supply volume [3,5,6]. They define technical or performance requirements for an OR air handling installation such as temperature, number of ACH or air volumes, type of OR air supply or UCV systems, and sometimes relative humidity [3,4,6,7]. National standards and guidelines in Europe are summarized in Table 1. The different OR air handling installations have various specifications and differ regarding costs. The Centers for Disease Control and Prevention (CDC) [15] describes higher installation costs for a UCV system and the WHO [14] state that a cost analysis by a European single hospital study (Italian study [16]) found a UCV system to be more expensive compared to a CV system.

The World Health Organization (WHO) [14] states that existing research on ventilation systems for operating rooms (ORs) is flawed and there is weak evidence [17–19] that Ultra Clean Ventilation (UCV) systems help to reduce Surgical Site Infections (SSIs). The financial costs of treating SSIs are increasing every year. Over the past decade, however, clear evidence [9,11,20] has been published contradicting WHOs view and recommending the use of a UCV-system rather than a conventional ventilation (CV) system to reduce the incidence of SSIs. According to the WHO and Centers for Disease Control and Prevention, the installation cost of a UCV-system is higher and more expensive than a CV-system [14,15].

This study aims to evaluate the capital and operational expenditures of different air handling installations with different [2] ultra-clean ventilation system and relate them to an air handling installation with a conventional ventilation system. Furthermore the study aims to compare the technical requirements of Dutch OR air handling installations with European national standards and guidelines, and the costs related to a surgical site infection with the capital expenditures studied.

This research can be used to support the decision-making process. Capital expenditures (CAPEX) and operating expenditures (OPEX) are becoming increasingly important. Before choosing an air handling and air supply system for the operating room, it is relevant to know the CAPEX and OPEX of different air handling and air supply systems and whether they meet national standards and guidelines. It is also relevant to know the return on investment if the incidence of a surgical site infection can be reduced by investing in an air handling installation with an ultra-clean air supply system.

2. Methodology

Our methodology is based on the study of Sdino et al. [21], were they defined four different phases: theoretical, practical, interactive and comparative. In our study in the theoretical phase, we analyzed and mapped the different European standards and guidelines. We also analyzed literature related to costs associated with surgical site infection. In the practical phase, we collected information from 24 hospital case studies where construction costs of operating room air handling installations and air supply systems were collected. Additional cost information was, by means of a questionnaire provided by healthcare consultants, manufacturers and installation companies collected in the interactive phase. In the comparative phase, we compiled all the information obtained.

In this study, the terms Conventional Ventilation (CV) system and Ultra Clean Ventilation (UCV) system are used to describe the method of air supply or air distribution in the operating room. We distinguish between an air handling installation (AHI) that supplies air to the conventional (CV) or ultra-clean (UCV) system and the installed CV or UCV system in the operating room.

Technical and financial data were collected from 24 hospitals built or under construction in the Netherlands from 2015 to 2022. In total, information on 166 ORs was analyzed.

Three air-handling installation typologies were defined; type A, type B, and type C (Fig. 1). Four OR air supply systems [2] were defined; Conventional ventilation (CV), controlled Dilution Ventilation (cDV), Temperature-controlled Air Flow (TcAF), and Uni-Directional Air Flow (UDAF). Detailed information on the functioning of these different air supply systems is described in the study on operating room ventilation systems [2]. The technical information of these systems was compared to national standards and guidelines (Table 1) in order to allow for a balanced CAPEX and OPEX comparison. Specifications of the air handling installations, system components, and requirements are described in Fig. 1 and Table 1.

The CAPEX of an air handling system type A was constructed from all components defined in Fig. 1 type A including a CV system which consisted of six standard High-Efficiency Particulate Air (HEPA) filter outlets, with HEPA H14 filter [22].

The CAPEX of an air handling installation type B and C was constructed from all components defined in Fig. 1 type B and C including one of the three different types of UCV systems; cDV, TcAF, or UDAF.

Table 1
Technical and requirement specifications air handling installation (AHI) and Conventional (CV) or Ultra Clean (UCV) systems according to national standards and guidelines in Europe.

National Standards or Guidelines	Classification type of operating room by standard/ guideline	Temperature [°C]	Relative humidity [%]	ACH or required air volume	Required CFU Level	Other requirement specifications	End Filter Supply air (EN 1822)
Norme Française (NF), France NFS90351	Zone 4a	19–26	Only required in certain conditions	≥6 outdoor air (ODA)	≤1 CFU/m^3	Unidirectional flow, discharge velocity ≥0,25–0, 35 m/s, ISO 5	HEPA H14
	Zone 3	19–26	Only required in certain conditions	≥15	≤10 CFU/m^3	Unidirectional flow or non-unidirectional flow, ISO 7	HEPA H14
	Zone 2	19–26	Only required in certain conditions	≥10	≤100 CFU/m^3	Non-unidirectional, ISO 8	HEPA H14
Health technical memoranda (HTM), England HTM 03-01	Ultra Clean	18–25	35–65	≥22	≤10 CFU/m^3 Ultra Clean Area	Own dedicated Air Handling Unit per OR and UCV min. 2.8 × 2.8 m	EPA E10
	Conventional	18–25	35–65	≥22		Own dedicated Air Handling Unit per OR	EPA E10
Deutsches Institut für Normung (DIN), Germany DIN 1946/4	1a	19–26	30–60	≥12,00 m^3/ h	Wound area ≤1 CFU/50 cm^2 Instrument table ≤1 CFU/50 cm^2	Advised UDAF size 3.2 × 3.2 m	HEPA H13/H14
	1b	19–26	30–60	≥12,00 m^3/ h		Recovery rate ≤20 min. DIN EN ISO 14644–3, 3,520/m^3 for 0.5 μm	HEPA H13/H14
Schweizerische Verein von Gebäudetechnik-Ingenieuren, Switserland SWKI VA105-01	1a	18–24	30–50	≥800 m^3/h		UDAF 9 m^2 Differential flow - Schutzgradmessung SG ≥ 2, 0/SG ≥ 4,0	HEPA H13
	1b	18–24	30–50	25 or ≥800 m^3/h		Recovery rate 100: 1 ≤ 20 min. SN EN ISO 14644-3	HEPA H13
Federatie Medisch Specialisten (FMS)/Vereniging Contamination Control Nederland VCCN RL7/RL 8, The Netherlands	1 +	18–23	<65	≥20	≤10 CFU/m^3	ISO 5, recovery rate 100: 1 ≤ 3 min. NEN EN ISO 14644-3	HEPA H13
FMS	1	18–23	<65	≥20		ISO 7, (complete OR) recovery rate 100: 1 ≤ 20 min. NEN EN ISO 14644-3	HEPA H13
FMS	2	18–23	<65	≥6		ISO 7 (complete OR), No recovery rate	HEPA H13
Swedish Institute for Standards (SIS), Sweden SIS TS 39; 2015	Infection-prone clean surgery	18–26	<70	≥0.56 m^3/s	≤5 CFU/m^3* - ≤10 CFU/m^3**	Mean Value ≤ 1.5 CFU/m^3 (highest value ≤ 5 CFU/m^3) *Clean air suits (everyone in the OR) Mean Value ≤ 5 CFU/m^3 (highest value ≤ 10 CFU/m^3) **Ordinary scrub suits (everyone in the OR)	HEPA H14

(*continued on next page*)

Table 1 (*continued*)

National Standards or Guidelines	Classification type of operating room by standard/ guideline	Temperature [°C]	Relative humidity [%]	ACH or required air volume	Required CFU Level	Other requirement specifications	End Filter Supply air (EN 1822)
	Other Surgery	18–26	<70	≥0.56 m^3/s	≤50 CFU/m^3* -≤100 CFU/m^3**	Mean Value ≤ 50 CFU/m^3 (highest value = ≤100 CFU/m^3) *Clean air suits (everyone in the OR) Mean Value ≤ 100 CFU/m^3 (highest value = ≤200 CFU/m^3) **Ordinary scrub suits (everyone in the OR)	HEPA H14

The CAPEX of five entire newly constructed operating room departments was also collected. These CAPEX consisted of the total construction cost of an operating room department, including ancillary areas such as corridors, changing rooms, airlocks, storage, and air handling installations for those areas. Only the entire complete newly constructed department projects were considered to allow for a balanced cost comparison. Total costs were normalized per OR, as for air-handling installations and air supply systems.

Operational expenditures (OPEX) were defined as costs related to maintaining the UCV systems according to the UCV manufacturer specifications and qualifying the systems yearly according to the national Dutch guideline [7]. This includes: 1) replacement of the HEPA filters every 5 years, 2) replacement of the laminar airflow diffusor for the UDAF every 10 years, 3) replacement of the air showers for the TcAF every 5 years, 4) replace the HEPA filters of the CV air supply filter air outlets after 5 years, 5) cost to technically qualify the OR CV and UCV air supply system yearly according to the national Dutch guideline [7] and 6) to determine the ultra-clean area of the UCV air supply system after every 5th year according to the national Dutch guideline [7].

3. Results

An OR with an air handling installation type A was not identified separately in this study, this is part of the basic construct of an operating room AHI. In our study we could extract from 54 ORs, out of the received data, the CAPEX of an air handling installation type A. 62 ORs had an air handling installation type B and 104 type C, all with a UCV system.

The mean amount of fresh supply air from the Make-up Air Unit (MAU) and Recirculation Air Unit (RAU) was 2,173 m^3/h and 7,683 m^3/h respectively (Table 2). The average total number of ACH (supply air to OR) was with 69 ACH higher than required by most national standards and guidelines [3,4,7,8] (Tables 1 and 2).

For the design conditions temperature, relative humidity, and type of end filter for the ORs in this study see Table 2. These design conditions were in line with the guidelines and standards for all ORs (Tables 1 and 2).

For 121 ORs we were able to equally compare the CAPEX (Fig. 2a) of the air handling installation types A, B, and C with a CV or UCV system. The CAPEX of a type A CV system was €89,715 per OR. The difference in CAPEX of an air handling installation type B with a UDAF system was €93,158 per OR. The additional CAPEX per OR of an air handling installation type C with a cDV was €62,491 with a TcAF €139,018 and with a UDAF €63,765, see Table 3. When compared to the total building cost of an OR, the CAPEX of an operating room AHI with a UCV air supply system versus a conventional system represented a 3–7% increase.

The yearly increase in OPEX of an operating room with a UCV system versus a CV system is between €281 and €783, calculated over a 5 years period and between €673 and €1,896, calculated over a 10 years period, see Fig. 2b and Table 4.

4. Discussion

The type of surgery, the internal heat load due to the medical equipment used, the number of people and clothing system, temperature and sometimes humidity requirements determine the needed air handling installation to supply the air to the OR and the type of the air supply system. The air handling installation and air supply systems in the current study all complied to the European standards and guidelines (Table 1). Therefore, insight in the costs of the different ventilation systems currently on the market is important. The results of this study indicate per OR an increase in capital expenditures (CAPEX) of €62,491 to €139,018 and an increase in yearly operational expenditures (OPEX) per year of €673 and €1,896 per OR of a UCV compared to a CV system calculated over a 10 years period.

The results of our study are in accordance with the results of Cacciari et al. [16]; CAPEX and OPEX increase when an air handling installation with a UCV system is installed in an OR compared to air handling installation with a CV system. However, the increase in their study is less compared to the increase in CAPEX and OPEX in the current study (see Table 3); they found an increase of 24% of the OR air handling system costs and an increase of 36% in annual operating costs (OPEX). The higher CAPEX can be explained by the fact that we collected data from 24 hospitals with different types of air handling installations and three types of UCV systems compared to one project with one type of UCV system as in the study by Cacciari et al. This study dated from 2004 and our study used data from 2015 to 2022. When compared to the total building costs the results in our study are in line with the results of Cacciari et al. (see

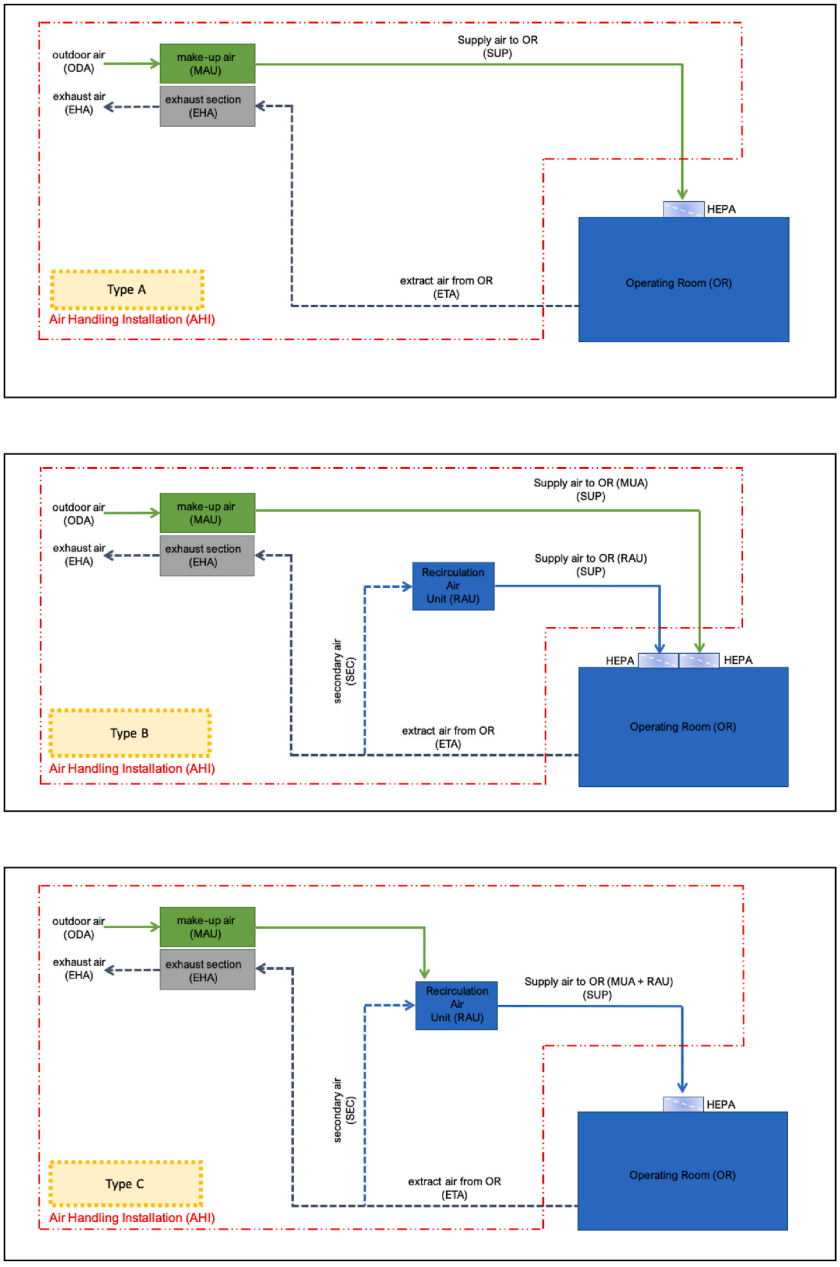

Fig. 1. Three typologies of OR air handling installations, type A, type B, and type C.

Table 4). In their study, the increase in CAPEX was only 5% compared to the total building costs of an OR [16]. In our study, the increase in CAPEX was, per operating room, between 3% and 7% depending on the type of air handling installation and UCV system.

In infection-prone surgeries where artificial implants are used, a level of ≤10 CFU/m^3 in the ultra-clean area [3,4,6,7] is recommended by most national standards and guidelines in Europe and used in scientific papers [10,23,24]. Recommendations to equip an operating room with an ultra-clean (UDAF) ventilation is not recommended by the WHO [14], CDC [15] and some studies claim UCV systems fail to prevent the incidence of surgical site infections (SSI) [24,25].

The WHO noted that existing research on OR ventilation systems is flawed and that there is only weak evidence that OR ventilation systems help in the reduction of SSIs [17–19]. However, in the last decade clear evidence has been published in peer-reviewed journals that contradicts this position. Several studies [9,11,20] advise to use a UCV system for infection-prone surgery [3,4,25] instead of a CV system [17,18]. UCV systems do reduce the number of CFUs in the OR [13,23,24] and do contribute to a lower number of SSIs [9,24]. In terms of micro-organism counts, ultra-clean air quality in the ultra-clean zone, should not exceed 10 CFU/m^3 [3,4,6]. To meet these micro-organism counts during infection-prone surgery, higher air volumes are introduced in the OR [9–11]. When lower air volumes are used, such as with a CV system, the number of micro-organisms in the whole OR will be higher [13,23],

Table 2
Technical specifications air handling installations (AHI) operating rooms of hospitals in the Netherlands per AHI typology and UCV system. Standard Deviation (SD).

No. ORs (n = 166)	Mean OR volume [m³]	Type Air Handling Installation (no. hospitals)	UCV Type	Temperature [°C]	Relative humidity [%]	volume MAU [m³/h]	No. ACH MAU	Air volume RAU [m³/h]	No. ACH total air volume
16	162	Type C (3)	cDV	min. 15 max. 23	min. 45 max. 70	2,213	15	7,178	64
47	178	Type C (9)	TcAF	min. 16 max. 24.5	min. >45 max. 70	2,014	14	6,376	56
54	129	Type B (9)	UDAF	min. 17.5 max. 24	min. >40 max. 70	2,458	21	7,734	78
49	156	Type C (4)	UDAF	min. 17 max. 24	min. 50 max. 65	2,000	13	9,046	74
					Mean total (SD)	2,173 (466)	16 (5)	7,683 (1,719)	69 (13)

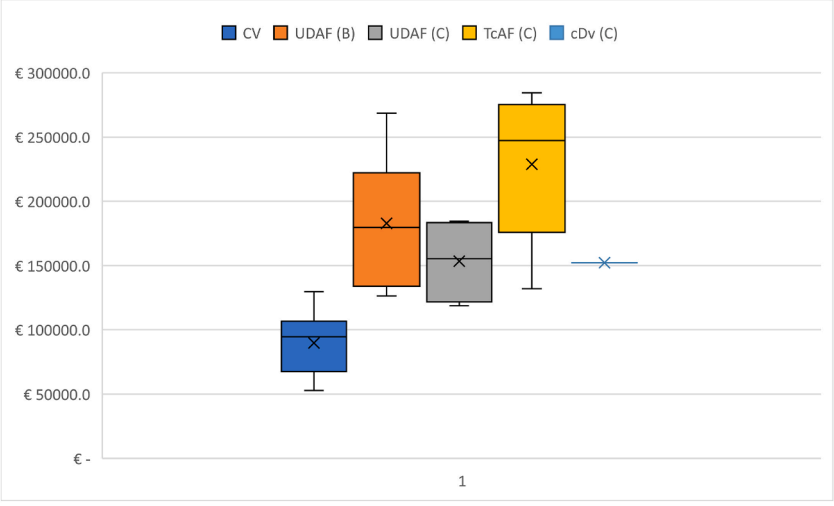

Fig. 2a. Capital Expenditures of an OR air handling installation type A, B and C with a CV or UCV system.

Table 3
Mean CAPEX per OR of the air handling installation typology A, B or C with a CV or UCV system and CAPEX of complete OR department. All mentioned expenditures in EUR, excluding VAT. Standard Deviation (SD).

CAPEX Air handling installation (AHI) per OR							CAPEX UCV system	CAPEX Air Handling Installation (type A, B, C) with CV or UCV air supply system					CAPEX OR department (n = 5)	CAPEX OR department per OR
MAU	Ductwork MAU	RAU	Ductwork per RAU	Controls MAU	Controls RAU	Total AHI per OR	UCV	AHI Type A with CV (SD)	AHI Type C with cDV	AHI Type C with TcAF (SD)	AHI Type B with UDAF (SD)	AHI Type C with UDAF (SD)	9,490,000	1,943,167
23, 971	33,239	17, 370	37,550	44,876	18,874	175, 878	38,520	89,715 (25, 145)	152, 206	228, 733 (56, 061)	182,872 (51,788)	153,480 (33,638)		
								+ **difference EUR. CAPEX CV to UCV per OR**						
									62,491	139, 018	93,158	63,765		

which is a risk factor for the incidence of SSIs [9,12]. In this study, all ORs had an air handling installation and OR UCV system installed with a mean of 69 ACH (see Table 2) and a mean total air volume of 9,857 m³/h.

The costs of treating SSIs are increasing every year. Prolonged length of stay of the patient in general wards or intensive care units (ICUs) as a result of an SSI was reported to constitute a major cost burden in multiple studies [14,26,27]. The infection risk for hip and knee arthroplasty is expected to increase from 2.18% [28] to 6.5% and 6.8% [29] in 2030, respectively. The additional cost of a surgical site infection per patient varies from €17,434 (France) to €32,000 (Italy) [24]. The majority of studies do not consider the wider

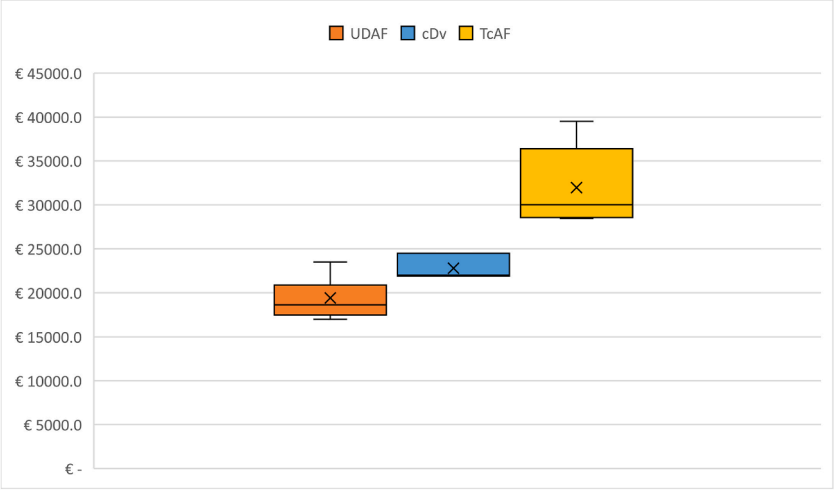

Fig. 2b. Operational expenditures of OR UCV systems, UDAF, cDV and TcAF over 10 years' time.

Table 4
Mean operational expenditures (OPEX) of CV and UCV systems. All mentioned expenditures in EUR, excluding VAT. Standard Deviation (SD).

OPEX	5 years CV	10 years CV	5 years cDV (SD)	10 years cDV (SD)	5 years TcAF (SD)	10 years TcAF (SD)	5 years UDAF (SD)	10 years UDAF (SD)
	5,750	13,000	9,667 (1,010)	22,800 (1,473)	9,417 (1,062)	31,960 (4,258)	7,154 (916)	19,726 (2,154)
+ difference EUR. OPEX CV to UCV			3,917	9,800	3,667	18,960	1,404	6,726

impact of SSIs on society like absence from work or reduced work productivity. In a period of 10 years, if only 2–4 infections can be prevented by implementing an ultraclean system, then its application is certainly worth considering.

According to the CDC, there is a relationship between SSIs and increasing antimicrobial resistance. Antimicrobial resistance is an urgent global public health threat [30]. With a higher proportion of resistant bacteria, the effect of antibiotic prophylaxis will be reduced. When taking into account the cost of a surgical site infection and the increasing antimicrobial resistance and thus the diminished effect of surgical prophylaxis, the additional investment in an OR air handling installation with a UCV system may be considered to prevent the incidence of SSIs during infection-prone surgery. Future studies should consider evaluating the potential reduction in SSIs and other health-related benefits associated with improved air quality.

This study has several limitations.

First, we did not take into account inflation rates. The costs received were those prevailing at the time the ORs in the hospital were built or when the OR department was renovated. External factors, such as changes in regulations, inflation, or variations in energy prices, are big uncertainties in cost estimation. Risk analysis should be conducted to identify all potential sources of cost increase or decrease.

Secondly, most of the air handling installations in the hospital were exclusively built for the OR department, in some cases, the air handling installation was used to supply air to other areas of the OR department. As a result, it was not possible to estimate exactly what the cost would have been if the air handling installation had been used only for the OR. Costs of the air handling installation could also vary because the numbers of ORs built differed per hospital, the manufacturer of the air handling installation control technology was not the same and the locations of the ORs relative to the plant room were not identical. The investment costs of the delivery and supply of cooling and heating needed for the air handling installations as well as the heating and cooling plants and their maintenance costs were not considered in this study. Some of those costs, such as maintenance and energy costs, may vary significantly between locations and over time.

Third, the OPEX can vary by hospital and region. Some hospitals have higher maintenance requirements for OR air handling installations and OR UCV or CV air supply systems than others. In this study, we took into account the maintenance specification of the UCV and CV system supplier or manufacturer. The mentioned OPEX relates only to the CV and UCV air supply system. Due to differences in the design and parameters of the complete OR air handling installation, heating and cooling systems, we could not include energy consumption and maintenance costs in the OPEX based on an equal costs comparison.

In the study on the ventilation effectiveness of different air supply systems we investigated the air quality and actual performance of UCV-systems and CV-systems [2]. Further research, e.g. on infection control, energy efficiency, and comfort, as well as the need for evidence-based comparison between the two types of air ventilation systems as described in this study, would be beneficiary to make informed decisions about air handling installations.

5. Conclusions

Choosing an air handling installations with an ultra-clean ventilation system over a conventional ventilation system, results in an increase in capital and operational expenditures. The capital expenditures for an air handling installation with an ultra-clean system represents an additional investment of about 3–7% of the total cost of building a completely new OR department. The operational expenditures of a UCV system represented an increase per operating room per year of €673 and €1,896 over the OPEX of an operating room equipped with a conventional system calculated over a 10 years period.

All Dutch operating rooms in this study complied to the technical specifications and requirements as described in the national European standards and guidelines. Therefore the results from this study can be used for other European countries as well.

When the impact on patient suffering and costs associated with surgical site infections are weighed against the costs associated with an air handling installation with an ultra-clean system, the investment is worth considering. If you can prevent two to four surgical site infections over 10 years, the investment will already be recovered.

This study provides relevant research focusing on the economic aspects of air handling installations and the different air supply systems in operating rooms. It provides valuable information to healthcare administrators, facility managers, and policymakers when making decisions about air handling installations and air supply systems for operating rooms.

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Author CRediT statements

J.L.A. Lans; Conceptualization, Ideas; formulation or evolution of overarching research goals and aims, Methodology, Development or design of methodology; creation of models, Validation, Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs, Formal analysis, Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data, Investigation, Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection, Resources, rovision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools, Data Curation, Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse, Writing - Original Draft, Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation), Writing - Review & Editing, Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages, Visualization, Preparation, creation and/or presentation of the published work, specifically visualization/data presentation, Project administration, Management and coordination responsibility for the research activity planning and execution, N.M.C. Mathijssen; Conceptualization, Ideas; formulation or evolution of overarching research goals and aims, Methodology, Development or design of methodology; creation of models, Validation, Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs, Formal analysis, Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data, Investigation, Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection, Resources, rovision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools, Data Curation, Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse, Writing - Original Draft, Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation), Writing - Review & Editing, Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages, Visualization, Preparation, creation and/or presentation of the published work, specifically visualization/data presentation, A.A.L. Traversari; Conceptualization, Ideas; formulation or evolution of overarching research goals and aims, Methodology, Development or design of methodology; creation of models, Validation, Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs, Formal analysis, Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data, Investigation, Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection, Resources, rovision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools, Data Curation, Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse, Writing - Original Draft, Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation), Writing - Review & Editing, Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages, I.M. Jacobs; Conceptualization, Ideas; formulation or evolution of overarching research goals and aims, Methodology, Development or design of methodology; creation of models, Validation, Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs, Formal analysis, Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data, Investigation, Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection, Resources, rovision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing re-

sources, or other analysis tools, Data Curation, Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse, Writing - Original Draft, Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation), Writing - Review & Editing, Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages, J.J. van den Dobbelsteen; Writing - Review & Editing, Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages, Supervision, Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team, M. van der Elst; Writing - Review & Editing, Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages, Supervision, Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team, P.G. Luscuere; Conceptualization, Ideas; formulation or evolution of overarching research goals and aims, Methodology, Development or design of methodology; creation of models, Validation, Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs, Formal analysis, Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data, Resources, rovision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools, Writing - Original Draft, Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation), Writing - Review & Editing, Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre-or postpublication stages, Supervision, Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team, Project administration, Management and coordination responsibility for the research activity planning and execution.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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