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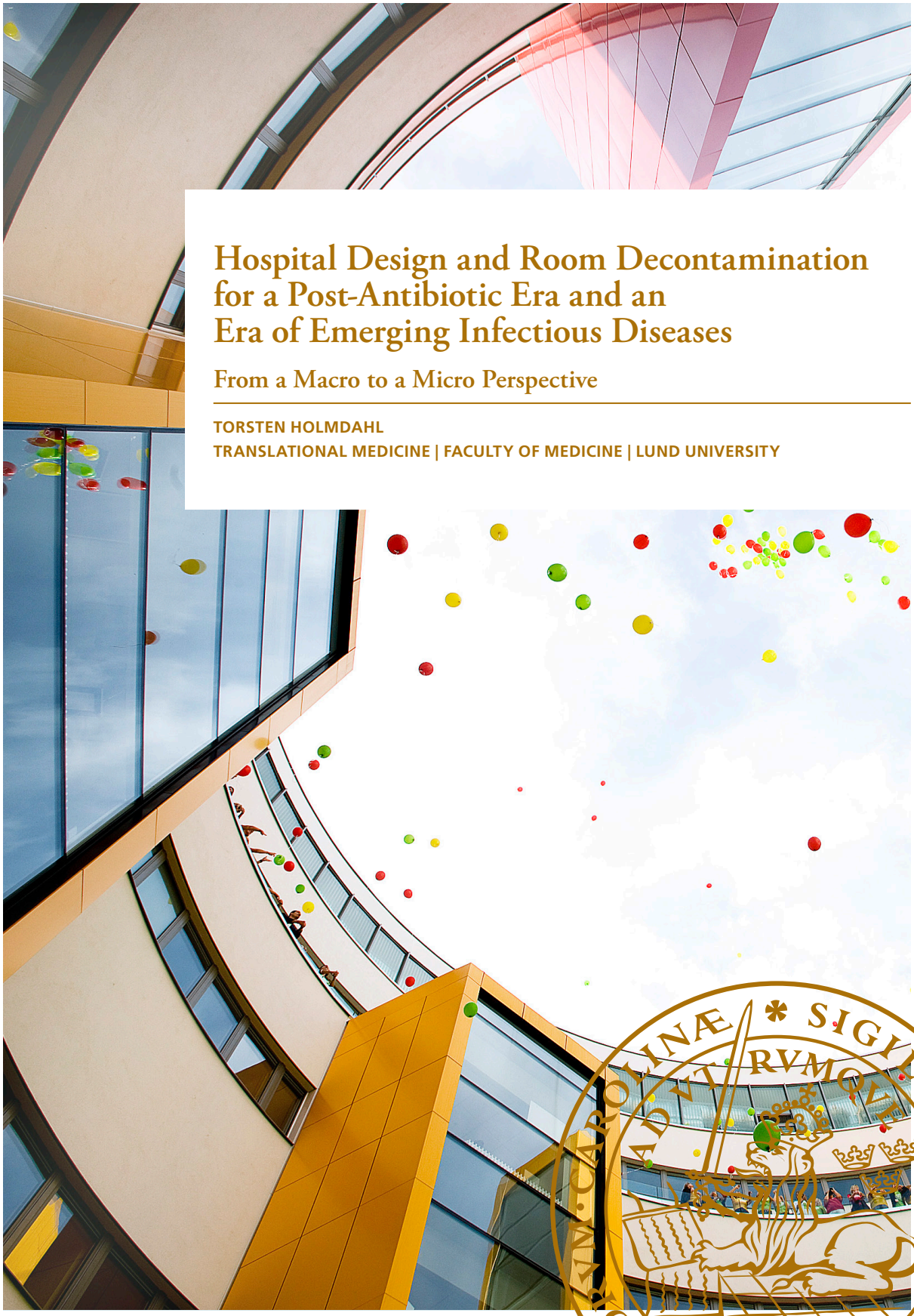

Hospital Design and Room Decontamination for a Post-Antibiotic Era and an Era of Emerging Infectious Diseases

From a Macro to a Micro Perspective

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TRANSLATIONAL MEDICINE | FACULTY OF MEDICINE | LUND UNIVERSITY

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LUND
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Title and subtitle Hospital Design and Room Decontaminatin for a Post-Antibiotic Era and an Era of Emerging Infectious Diseases. From a Macro to a Micro Perspective

Abstract

Background: Antimicrobial resistance, healthcare-associated infections, and emerging infections are serious threats to humankind and represent important challenges for healthcare in the future.

Many hospitals in the world were built in the 1970s and are now outdated, and hence a huge boom in building of new hospitals is clearly imminent. In this context, considering the residual contamination with microorganisms that occurs after conventional cleaning and disinfection, there is a need for more efficient decontamination.

Design: A case study of the planning and construction of a new infectious diseases facility in Malmö was undertaken.

Subsequently, in a full-scale hospital patient room, we performed a head-to-head investigation of two different hydrogen-peroxide-based no-touch decontamination systems, and thereafter an additional study to analyze the effectiveness of hydrogen peroxide for inactivation of calicivirus.

Finally, we compared the impact of hydrogen peroxide on noroviruses by quantitative PCR (qPCR) assessment of viral RNA levels and evaluation of viability by cytopathogenic effect, and replication of intracellular minus-strand RNA.

Results: Use of a full-scale mock-up can be beneficial. The flow or movement of patients with contagious diseases should be organized in ways that reduce the risk of transmission.

Hydrogen peroxide vapor (HPV) was more potent than aerosolized hydrogen peroxide (aHP), measured as efficiency in killing *Geobacillus stearothermophilus* spores used as biological indicators. Neither feline calicivirus nor murine norovirus (used as surrogate markers for human norovirus) was recovered after HPV treatment. We also noted that after HPV treatment, there was only a minor decline in quantitative PCR levels, despite full viral inactivation measured as tissue culture infectious dose 50% (TCID50) or detection of intracellular minus-strand replicating RNA.

Conclusions: Numerous actions from the macro to the micro level must be taken to address the problem with spread of infections and antimicrobial resistance at healthcare settings.

Infection control should always be regarded as an essential aspect when planning construction of new hospitals. HPV is more efficient than aHP and can be used for terminal decontamination of bacteria, spores, and viruses commonly found in hospitals.

The successful eradication of the two surrogate viruses suggests that HPV can be a useful tool for decontamination of surfaces contaminated with norovirus in patient rooms and thereby prevent nosocomial spread to subsequent patients.

Norovirus inactivation by hydrogen peroxide can not be measured by qPCR.

Key words Hospital Design, Room Decontamination, Norovirus, Hydrogen Peroxide

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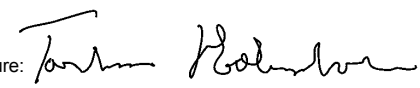
Signature:  Date: August 7, 2017

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To my family: Charlotte, Sofie, Martin and Linn

Content

List of Papers

This thesis is based on the following papers, refered to in the text by their Roman numerals:

I. **Holmdahl T**, Lanbeck P. Design for the Post-Antibiotic Era: Experiences from a New Building for Infectious Diseases in Malmö, Sweden. HERD. 2013 Summer; 6(4):27-52.

II. **Holmdahl T**, Lanbeck P, Wullt M, Walder M. A Head-to-Head Comparison of Hydrogen Peroxide Vapor and Aerosol Room Decontamination Systems. Infect Control Hosp Epidemiol. 2011 Sep; 32(9):831-6.

III. **Holmdahl T**, Walder M, Uzcátegui N, Odenholt I, Lanbeck P, Medstrand P, Widell A, Hydrogen Peroxide Vapor Decontamination in a Patient Room Using Feline Calicivirus and Murine Norovirus as Surrogate Markers for Human Norovirus. Infect Control Hosp Epidemiol. 2016 May; 37(5):561-6.

IV. **Holmdahl T**, Odenholt I, Riesbeck K, Medstrand P, Widell A. Hydrogen Peroxide Vapor Treatment Inactivates Norovirus But has Limited Effect on Post-Treatment Viral RNA Levels.

Under revision

Populärvetenskaplig sammanfattning.

Hur skall sjukvården och samhället hindra spridning av farliga sjukdomar när antibiotika förlorar sin verkan i kampen mot smittsamma sjukdomar?

Ökande antibiotikaresistens, nya infektioner, infektioner i ny skepnad eller i ökande frekvens samt sjukhusförvärvade infektioner är reella hot mot mänskligheten och framtidens sjukvård. Ett av våra främsta vapen mot allvarliga smittsamma sjukdomar i dagens sjukvård är antibiotika. Tyvärr är vi på väg mot en situation där antibiotika förlorar i verkan och effektivitet. Detta skulle få förödande konsekvenser för enskilda individer och hela samhället.

Vi anser att det är hög tid för sjukvården och samhället att förbereda sig inför den nya situationen, som vi i detta avhandlingsarbete betecknar den ”postantibiotiska eran”. Det är nu under de närmaste åren, som vi har chansen att förbereda oss.

Från ett makro- till ett mikroperspektiv har vi i fyra artiklar studerat effekterna av övergripande sjukhusdesign och mera specifika åtgärder för att begränsa smittspridning i en postantibiotisk era.

Många sjukhus i världen och i Sverige är byggda på 1970-talet. De är gamla och slitna. Därför kommer det under de närmaste åren att ske en massiv satsning på nya sjukhusbyggnader. Det gäller då att ta chansen att bygga rätt ur vårdhygienisk synpunkt. I den preantibiotiska eran, det vill säga innan det fanns verksamma antibiotika, byggdes sjukhus ofta med avsikt att förebygga infektioner och understödja god hygien. Sjukhus byggdes i paviljonger med mycket utrymme, luft och ljus samt självdrag. Infektionskliniker eller epidemisjukhus byggdes i allmänhet utanför sjukhusområdena eller i utkanten av dessa. De hade ofta ingång från utsidan till patientrummen.

Efter andra världskriget och fram emot 1970 talet byggdes sjukhus alltmer i centralblock, influerade av industriell produktion och med tonvikt på effektiva patientflöden. Samtidigt fick man alltfler effektiva antibiotika. Infektionsproblemen hamnade då i bakgrunden.

Det gäller nu när vi närmar oss den postantibiotiska eran att använda erfarenheter från den preantibiotiska tiden, men i en moderniserad tappning och med användande av modern teknik.

Inspirationen till detta synsätt som nu resulterat i föreliggande avhandling fick vi 2005 i samband med planeringen av en ny infektionsklinik i Malmö. Det var då längesedan, det byggts en helt ny infektionsklinik i Sverige. Samtidigt ökade hoten om tilltagande antibiotikaresistens och så kallade ”emerging infections”. Med detta begrepp avses nya infektioner eller gamla infektioner som blossat upp och ökar i frekvens eller ändrar skepnad. Exempel är SARS, pandemisk influensa och vinterkräksjuka.

Erfarenheterna från SARS utbrottet 2004 påverkade oss mycket. Vi tog då vi emot patienter med misstanke om denna då okända, smittsamma, sjukdom i slitna och icke ändamålsenliga lokaler. Samtidigt kom det rapporter om spridning mellan patienter och till personal från andra delar av världen.

Lyckligtvis blev det ingen spridning i Sverige men det lärde oss att beredskap för okända smittsamma sjukdomar är viktigt.

Som infektionsläkare beslöt vi oss för att vara djupt involverade i planeringsprocessen av den nya kliniken, eftersom vi bedömde att infektionskunnande och vårdhygienkunskaper var särskilt viktiga i denna typ av byggprocess. Vi genomförde litteraturstudier, nationella och internationella studiebesök och kom bland annat i kontakt med begreppet "evidence based design". Ett begrepp som innebär att sjukhusbyggnation skall baseras på forskning på samma sätt som medicinska behandlingar.

Viktiga kunskaper för bättre sjukhus

Förberedelserna och byggprocessen dokumenterades noga och dessa erfarenheter samlades ihop i en beskrivande fallstudie. Denna artikel utgör arbete I.

I artikeln beskrivs planeringsprocessen bakom den nya infektionskliniken.

Vi understryker betydelsen av att vi som infektionsexperter fått vara delaktiga i processen och vikten av att vårdhygien betraktas som en betydelsefull del i planeringen av sjukhusbyggnationer.

Vi beskriver vikten av separat ventilation och hur man separerar flödena av smittsamma patienter från övriga patienter. Samtidigt poängteras vikten av att infektionskliniker är belägna centralt på sjukhusen.

Betydelsen av standardisering och flexibilitet diskuteras också.

Att använda sig av ett fullskaligt provrum visade sig ha många fördelar. Kostsamma misstag kunde undvikas under byggprocessen. Dessutom fick personalen möjligheter att prova ut om arbetsrutinerna fungerade i den nya lokalen och kunde sedan påverka utformningen.

Provrummet kom sedan att användas för vårdhygienisk forskning kring nya avdödningstekniker mot mikroorganismer i sjukhuslokaler. När den nya kliniken stod färdig och provrummet rivits kunde vi flytta över denna verksamhet till den gamla utrymda infektionskliniken.

Väteperoxid förbättrar smittstädning.

Begreppet ”No touch decontamination” blev då aktuellt. Bakgrunden är att manuell städning är mycket svår att standardisera och att man trots manuell städning finner kvarvarande smittämnen i ett patientrum. Trots städning föreligger en fördubblad risk för en ny patient att smittas med föregående patients sjukdom eller bärarskap av resistenta bakterier.

”No touch decontamination” innebär att en icke manuell, generell och automatiserad metod för smittstädning samt dekontamination används. Tillgängliga metoder är bland annat UV-ljus, ozon och väteperoxid i två olika distributionsformer. Av dessa metoder fann vi väteperoxid vara mest intressant ur effektsynpunkt. UV-ljus är atoxiskt och snabbt men är behäftat med skuggeffekter och är mindre effektivt. Ozon är toxiskt och mindre effektivt, bland annat på grund av att det har en mycket ytlig effekt.

Första jämförande studien av metoder med väteperoxid i ett fullskaligt patientrum

Vi har i arbete II utfört den första jämförande studien mellan två robotbaserade system för att sprida väteperoxid i vårdlokaler. Dessa bygger på två olika principer: väteperoxid i ångform, hydrogen peroxide vapor (HPV), respektive väteperoxid i aerosolform, aeroslized hydrogen peroxide (aHP). Studien utfördes ett fullskaligt patientrum. Vi har mätt systemens förmåga att avdöda biologiska indikatorer med Geobacillus steathermophilus-sporer som är några av de mest svåravdödade mikroorganismerna. Standardiserade sporprover var då utplacerade på olika, delvis svåråtkomliga ställen i olika höjd, både i patientrum och hygienutrymmen.

Tre försöksomgångar genomfördes. HPV visade sig vara mest effektivt och ha mest reproducerbart resultat, med fullständig avdödning i alla tre testomgångarna jämfört med 10% i första omgången och 79% i påföljande två testomgångar för aHP . HPV var samtidigt den snabbaste metoden, med en tidsåtgång på cirka 3 timmar.

Väteperoxid är miljövänligt, då det bryts ner till syre och vatten och det har ingen skadlig inverkan på rumsinredning eller apparatur. Dock är det toxiskt för människor och rummet måste förseglas med tejp under behandlingen. Koncentrationen av väteperoxid måste mätas innan man kan beträda rummet igen.

Positiva effekter mot vinterkräksjuka

Spridning av vinterkräksjuka, som orsakas av calicivirus vars största undergrupp är norovirus, utgör för närvarande ett stort problem inom sjukvården. Smittdoserna är låga och virus överlever länge i miljön. Konventionell rengöring har otillräcklig effekt. Dessutom är utvärdering av rengöring/dekontamination svårvärderad, då detta virus inte kan odlas på något enkelt sätt.

Felint (katt-) calicivirus (FCV) respektive murint (mus-) norovirus (MNV) har i olika sammanhang använts som surrogatmarkörer (ersättning) för humant norovirus (HuNV) i forsknings sammanhang.

Vi har i arbete III använt olika cellodlingssystem för både FCV och MNV. Vi gjorde därefter tester i fullskaliga patientrum. För respektive virus gjordes tre separata testomgångar. Virus torkades in i brunnar i plastplattor och placerades ut på delvis svåråtkomliga ställen i rummet. Rummet HPV-behandlades sedan. Motsvarande försök gjordes i ett obehandlat rum. Avdödning av virus mättes sedan i ett cellodlingssystem.

En fullständig avdödning uppmättes i det behandlade rummet medan virus kunde odlas fram ifrån det obehandlade rummet.

HPV skulle således kunna användas för att förhindra spridning av vinterkräksjuka på sjukhus.

Mänskligt calicivirus gick till helt nyligen inte att odla och är fortfarande svårodlat. Därför, får man i vårdhygienisk forskning förlita sig till mätning med PCR, en metod som kan påvisa RNA (genetiskt material) från dessa virus. Med PCR går det till skillnad från odlingsbaserade metoder inte att avgöra om det är ”dött virus” eller virus som kan föröka sig, dock är det möjligt att mäta virusmängden med så kallad kvantitativ PCR (qPCR).

I arbete IV söker vi svar på frågan om det går att mäta behandlings-effekt/inaktivering av HuNV, orsakad av väteperoxid med hjälp av kvantitativt PCR (qPCR).

Väteperoxidens effekt på qPCR nivåer av HuNV (två genotyper) jämfördes med motsvarande effekt på MNV.

Avdödningen av det odlingsbara viruset MNV mättes samtidigt med cellodlingsbaserade tekniker. Vi använde oss då bland annat av mätning av minussträngat RNA, en markör för aktiv virusförökning. Vi förutsatte att människans och musens calicivirus är så biologiskt lika att resultaten även avspeglar avdödning av det humana viruset.

Resultaten i denna studie var att avdödning med väteperoxid hade mycket liten effekt på qPCR-nivåerna, medan avdödningen mätt med cellodlingsteknik var total. Således kan avdödningseffekten inte avläsas i nedgång i qPCR nivåer.

Sedan kan man utifrån denna studie resonera kring om resultaten är generaliserbara, det vill säga om qPCR nivåerna även för andra rengöringsmetoder säger något om avdödningen.

Många samverkande åtgärder krävs i den postantibiotiska eran

För att klara av utmaningarna inför den postantibiotiska eran krävs både nya metoder och en utvärdering av tidigare använda metoder. Erfarenheterna från spridning och bekämpning av smittsamma sjukdomar bör beaktas i all metodutveckling.

Kunskapen om infektionssjukdomar och vårdhygien har blivit allt viktigare och bör uppmärksammas mer i alla beslut om nya sjukhusbyggnationer.

Abbreviations

aHP	aerosolized hydrogen peroxide
AMR	antimicrobial resistance
ATP	adenosine triphosphate
BI	biological indicator
CPE	cytopathogenic effect
Ct	cut off threshold
EBD	evidence-based design
ESBL	extended-spectrum beta-lactamase
FCWF	*Felis catus* whole fetus (designation for a feline permissive fetal cell line)
FCV	feline calicivirus
GI	genogroup I
GII	genogroup II
HAI	health-care associted infections
HPV	hydrogen peroxide vapor
HuNV	human norovirus
MERS	Middle East respiratory syndrome
MNV	murine norovirus
MRSA	methicillin-resistant *Staphylococcus aureus*
NTD	no-touch decontamination
PCR	polymerase chain reaction
p.i.	post infection
ppm	parts per million
PX-UV	pulsed xenon ultraviolet light
qPCR	quantitative PCR
SARS	severe acute respiratory syndrome
SUS	Skåne University Hospital (in Swedish: *Skånes universitetssjukhus*)
TCID50	tissue culture infectious dose 50%
UVC	ultraviolet light wavelength C

VRE	vancomycin-resistant *enterococci*
WHO	World Health Organization

Preface

When plans were being made to build a new infectious diseases facility in Malmö, it had been quite some time since any new centers of this type had been established in Sweden. Opening of the unit in Malmö created a strong demand for information about the process leading to creation of this facility. Accordingly, we decided to gather data and write a descriptive report detailing the process, which initiated the work underlying this thesis. As part of the planning process, a full-scale mock-up of a hospital patient room was constructed. Thereafter, we used this model room in infection control research, which raised our interest in “no-touch” decontamination (NTD) and led us to perform a head-to-head study of the effects of two different hydrogen peroxide systems on bacterial spores. Experiences from the first investigation prompted us to address the problem of nosocomial norovirus infections and decontamination. This short description illustrates how our journey from macro to micro began.

.

1 Background

At a high-level meeting on antimicrobial resistance held by the General Assembly of the United Nations in September 2016, Dr. Margaret Chan[1], Director General of the World Health Organization (WHO), said the following: "Antimicrobial resistance poses a fundamental threat to human health, development, and security." More recently, Dr. Chan called the Ebola outbreak in 2014–2016 "the largest, most complex and most severe we've ever seen"[2].

1.1 Antimicrobial resistance

Are we on our way to a post-antibiotic era?

Antimicrobial resistance (AMR) is a growing problem globally. In April 2014, the WHO declared "that a post antibiotic era in which common infections and minor injuries can kill is a very real possibility for the 21st century"[3].

A British report has estimated that at present roughly 700,000 deaths occur annually worldwide due to infections caused by drug-resistant microbes, and that that number will rise to more than 10 million by 2050[4]. Antibiotic resistance has been increasing ever since the golden era stretching from the discovery of penicillin and sulfa drugs to the 1960s. Indeed, Fleming and Flory had already warned of this danger as early as 1945, when they were given the Nobel Prize in Medicine[5].

Figur 1 Sir Alexander Fleming receiving the nobelprice from the hands of his majesty Gustav V 1945. Photographer unknown. Photo from Wikipedia.

Penicillin was initially considered a miracle drug, and it saved many lives during and near the end of World War II. In short, the development of new antibiotics saved countless lives by enabling treatment of serious infections, and these drugs were also fundamental for the development of modern healthcare including advanced surgical operations, intensive care, and immunosuppression.

All use of antibiotics contributes to development of resistance, and sooner or later resistance will be induced against every new antibiotic that is introduced. Resistance is caused by a natural process of mutations, and the ability to develop resistance to antibiotics emanates from genes that have existed in microorganisms for millions of years. Due to the extensive use of antibiotics, the development of resistance to these drugs is occurring at a faster rate than the development of new antibiotics[6, 7]. One of the impediments limiting the production of novel antibiotics is insufficient incentive for the pharmaceutical industry, because antibiotics are given in short courses and infectious diseases physicians and guidelines advise restrictiveness in prescribing new antibiotics. A potential solution that is being discussed includes a partnership between industry and academics and public global funding of antibiotics research[7].

After the introduction of penicillin, the problems related to antimicrobial resistance initially involved gram-positive bacteria and penicillin-resistant (penicillinase-producing) *Staphylococcus aureus*, and thereafter methicillin-resistant *S. aureus* (MRSA). In the 1960s and later vancomycin-resistant enterococci (VRE) and penicillin-resistant pneumococci. Today the fastest growing obstacle is resistance of gram-negative bacteria with extended-spectrum beta-lactamases (ESBLs) and even worse ESBL producing bacteria with resistance to carbapenems (ESBL carba), which constitute a class of relatively modern antibiotics exhibiting the broadest spectrum. We are now confronted with bacteria with very few or no treatment options, examples of which include multi-resistant isolates of *Neisseria gonorrhoea,*

Enterococcus faecium, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aureginosa.* Older antibiotics such as colistin are being put to use again, but resistance to these drugs is also occurring[8].

There are two important factors behind antibiotic resistance: the **overuse** of antibiotics, which creates selection of resistant bacteria, and the **spread** of both resistant bacterial strains and resistance mechanisms between bacteria (e.g., via plasmids). Overuse is a problem in humans, and this also applies to livestock, among which overuse is even more extensive[9]. Actions taken to diminish the use of antibiotics include the following: surveillance programs for AMR and antibiotic prescription; information campaigns to shift public demands for antibiotics; antibiotic stewardship; regulations for use of antibiotics in livestock, because resistant bacteria are transmitted from farm animals to humans[9]. Among other measures taken are vaccinations against bacterial infections. The use of antibiotics may also be decreased by vaccinations against viral infections that can precede bacterial infections, as well as by improved diagnostic tools that can discriminate between bacterial and viral infections.

Spread of resistant bacteria occurs in both community and healthcare settings. Today the majority of transmission events take place in society in general. However, the spread in the healthcare environment might have an even greater impact, because such surroundings represent a mixing vessel for fragile patients with weak immune systems, a large proportion of whom are on antibiotics. There is also an important crowding factor in healthcare settings. MRSA, VRE, and *Acinetobacter* are examples of resistant bacteria that can survive on surfaces for long periods of time and thereby create a greater risk of transmission in healthcare settings. *Enterobacteriaceae* survive for a shorter time on surfaces and are spread primarily via direct contact[10].

Antibiotics and the ability to prevent infections with prophylaxis and to treat infectious complications are fundamental in aspects of modern healthcare such as prosthesis surgery, intensive care, immunosuppression for transplantations, and immune-suppressive therapy in oncology, hematology, and the treatment of autoimmune diseases.

In conclusion, resistance to antibiotics is rapidly increasing. To be able to stop this process, it is necessary to quickly implement numerous actions in all parts of the world, because bacteria do not respect national borders.

In conclusion, resistance to antibiotics is rapidly increasing. To be able to stop this process, it is necessary to quickly implement numerous actions in all parts of the world, because bacteria do not respect national borders.

1.2 Health-care associated infections (HAIs)

Historically, most patients were treated and cared for outside hospitals, and only poor and disadvantaged people were hospitalized, because such institutions were considered to be dangerous places connected with the risk of spread of contagious diseases[11].

Ignaz Semmelweis was a pioneer in infection control, and he noted that it was more likely for fever to occur in women who gave birth in hospitals than in those who gave birth outside such facilities. Semmelweis also observed a significant difference in infection-related mortality between what he classified as childbirth divisions I and II. He observed the highest mortality in division I, and found that medical students active in that category often performed autopsies before assisting in deliveries, whereas that did not apply to midwives in division II who helped with deliveries. Semmelweiss hypothesized that hand disinfection could prevent transmission from a diseased corpse to a pregnant woman. In May 1847, it was decided that all medical students should wash their hands in chlorinated lime before assisting in deliveries, and thereafter the mortality rate fell dramatically. Semmelweiss's work was highly disputed upon publication, and he eventually became psychotic and died from streptococcal sepsis in an asylum[12].

Florence Nightingale was also a pioneer in hospital design and infection control. She observed that open windows allowed air from the wards to pass into the corridors, and she believed that respiratory secretions were potentially dangerous, especially among the sick. In her words, "Depriving patients of appropriate ventilation is nothing but manslaughter under the garb of benevolence"[13]. She also came to the conclusion that sick patients should be isolated and that hospitals should be no more than two stories high, assuming that taller buildings interfere with sunlight and ventilation[13]. Moreover, Nightingale recorded disparities in healthcare-associated mortality at different hospitals in England, and noted the highest levels of poor health at the large hospitals in the central part of the country. In notes on hospitals[13], she wrote: "A poor sufferer would have a better chance of recovery if treated at home."

She also worked in cooperation with Registrar General William Farr, who became the first health statistician in England. Together, Farr and Nightingale showed excess mortality due to infections among hospital employees compared to other individuals, indicating that contagious diseases were spread at hospitals[13]. Nightingale and Farr also demonstrated that contagious diseases constituted the main cause of death in the Crimean War, and their work led to improved hygienic practices and significantly lower mortality[14]. All this was achieved before it was known that bacteria were the cause of the problems.

Another early example of both registration and the risk of bringing together patients in hospitals is illustrated by observations made by Dr. James Simpson, who compared amputations performed at city hospitals with those conducted by country practitioners in 1860[15, 16]. Simpson chose to evaluate amputations, because such operations were easy to compare and did not depend on surgical skills. Simpson measured results in terms of survival and found that amputations done by country practitioners were five times as likely to be successful due to fewer deaths caused by infectious complications. Furthermore, he showed that hospital size was proportional to mortality, and observed that the fewer patients per room, the less likely infections would spread to other patients, thus supporting the argument against crowding and concentration of sick people.

1.2.1 Registration and definition of HAIs

It is evident that registering HAIs by measuring incidence or prevalence of these infections is very important to discern differences over time both within a single facility and between facilities. These data can subsequently be used to identify causes and change methods and behavior. Research has also shown that registering and giving feed back on results regarding incidence and prevalence can lead to improvement even without officially changing routines[17]. The use of clear definitions is a central aspect in this context.

HAI is defined by the WHO as an infection acquired in a hospital or healthcare facility by a patient who was being treated for some reason other than infection and the infection was not present or incubating at the time of admission. This includes infections acquired by patients while in the hospital but appearing after discharge, as well as infections contracted by healthcare staff[18].

Swedish point prevalence studies and Swedish health and welfare authorities define HAIs as any of the following[19]: postoperative infections occurring within 30 days of surgery or within 1 year after implantation surgery; device-related infections due to central venous catheters, urinary tract catheters, ventilator treatment, endotracheal tubes, or indwelling cerebral ventricular drainage; drug-related infections defined as *Clostridium difficile* enteritis and infections associated with chemotherapy for cancer or other immune-modulating drugs or corticosteroids; other infections occurring > 48 hours after admission.

1.2.2 HAIs make a hospital a dangerous place

HAIs constitute the leading cause of care-related morbidity and the most prominent patient safety issue, and they also cause more deaths than traffic accidents and breast

cancer[20, 21]. HAIs have an impact on approximately 6–10% of all hospitalized patients in most countries. In the European Union, about 4 million people are annually affected by HAIs, and such infections are directly related to 37,000 deaths and represent a contributing factor in around 110,000 deaths[22]. Furthermore, HAIs increase the length of hospital stays and the number of readmissions, and also cause considerable suffering and invalidity and are very costly[19].

In Sweden, a point prevalence measurement of HAIs (based on recording on one single day) has been performed biannually since 2008 until 2013 and once a year at all hospitals since 2014. The prevalence during this period has been stable at around 9%[23]. Data on risk factors such as central venous catheters, surgical operations, urinary catheters, mechanical ventilation, immunosuppression, and antibiotics are also recorded[23].

HAIs can be endogenous or exogenous, but also secondary exogenous, indicating that exogenous bacteria are introduced and integrated in the normal flora of the patient and later give rise to an infection. The majority of HAIs are endogenous, which means that a person is infected by his/her own bacteria[24]. The most common HAIs are pneumonia, urinary tract infections, and wound infection[23]. Other examples of infections that can be associated with healthcare are influenza, viral gastroenteritis, *C. difficile* infections, and blood infections like hepatitis[10]. Patients with an impaired immune status and indwelling catheter are more prone to HAIs. Most HAIs are endemic but can under some circumstances cause outbreaks in a hospital ward; in such cases, it can be useful to perform molecular typing of the isolated microorganisms to identify the source of the infection.

1.2.3 Interaction between HAIs and AMR

Antibiotic resistance aggravates the problems created by HAIs by making it more difficult to treat the infections (e.g., MRSA, VRE, and ESBL). HAIs also lead to higher consumption of antibiotics, which contributes to development of antibiotic resistance. Patients on antibiotics are more prone to HAIs than non-antibiotic-treated patients, and hence the issues of HAI and AMR are firmly linked together.

…the issues of HAI and AMR are firmly linked together.

1.2.4 Transmission

The two major routes of spread of microorganisms in hospitals are contact transmission and airborne transmission[10], which can be further divided into direct

or indirect transmission. Direct contact transmission entails dissemination directly from one patient (e.g., from an infected wound) to another. Direct airborne spread describes microbes that directly reach the eyes or mucosa of the recipient. Indirect transmission involves transfer of microorganisms from one person to another via hands, surfaces, handles, or equipment, and this category also includes fecal–oral transmission.

In airborne infections, infectious particles fall onto surfaces and are manually picked up by other patients or healthcare staff. In **indirect contact transmission**, contagious agents are transferred from one person to surfaces and then taken up by another person who touches the contaminated surfaces. Thus, in both airborne infections and indirect contact transmission, contaminated surfaces can serve as an intermediate reservoir of infectious particles.

Airborne transmission usually occurs either via droplets (i.e., larger particles that are conveyed as far as about a meter) or via aerosols (i.e., finer particles in a gas that can be conveyed farther and for longer periods of time)[25]. An extreme example of aerosol transmission is the foot-and-mouth disease virus, which has been found to cross the English Channel[26]. The cutoff between droplet and aerosol spread is commonly set at 5 μm[27]. Nevertheless, there is currently some controversy regarding the size at which the cutoff should be stipulated, considering that it also depends on temperature and humidity, and a particle can change density during transmission. Particles < 10 μm are more prone to reach the alveoli[27]. Aerosols and droplets can be produced by breathing, coughing, sneezing, and talking and can contain respiratory pathogens[27]. Vomiting, diarrhea, and toilet flushing can also contribute to aerosol formation and spread of gastrointestinal microorganisms[25]. *C. difficile* spores and noroviruses have a potential for airborne dispersal[28, 29].

Varicella and measles often spread via aerosols, and tuberculosis is notable for airborne spread despite the larger size of the bacteria. Influenza and more common airway viruses can also be disseminated via aerosols as well as droplets[30], although transmission often occurs via handcontact. Furthermore, influenza virus, adenovirus, RS virus, rotaviruses, and caliciviruses can survive on surfaces for long periods of time[31, 32]. Skin flakes can be airborne carriers of bacteria that are later precipated[10], and this route is increased for patients with wounds (e.g., those with burns can be heavy spreaders[33,]) and can also be elevated during activities such as making beds[34].

In conclusion, surfaces are considered increasingly important for the spread of HAIs and AMR.

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1.2.5 HAIs and AMR: implications for design and organization of healthcare facilities

It is essential to bear in mind the features of spread of antimicrobial resistance and HAIs when considering the organization of healthcare and construction of new medical facilities. Examples of negative factors that should be avoided are overcrowding[35], understaffing[36, 37], and patient flows with mixing of contagious and non-contagious patients. Important preventive factors include a sufficient number of single rooms[38, 39], and the possibility of isolation management, and on a daily basis also adherence to infection control measures such as hand hygiene and correct dress code[40, 41]. To improve compliance with hand hygiene, it is essential to ensure strategic placement and a greater number of stations for hand washing and alcohol dispensers[42-44]. The quality of the cleaning of hospitals is also a critical factor, and therefore surfaces must be easy to clean[11,45-47].

The implications of hospital design for airborne spread of infectious microorganisms include the importance of adequate ventilation, isolation possibilities, and separate flows of contagious and non-contagious patients, and the knowledge that airborne transmission is linked to transmission via surfaces.

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• the importance of adequate ventilation
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1.3 Emerging infections

Emerging infections can be defined either as the introduction of new infections that are in some cases caused by pathogens not previously identified in a particular species or as previously known infections that are altered or have returned, increased in number, and are becoming more important (called re-emerging infections). Examples of emerging and re-emerging infections that influenced assessments in the present project in different ways include SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), Ebola, pandemic influenza, and norovirus.

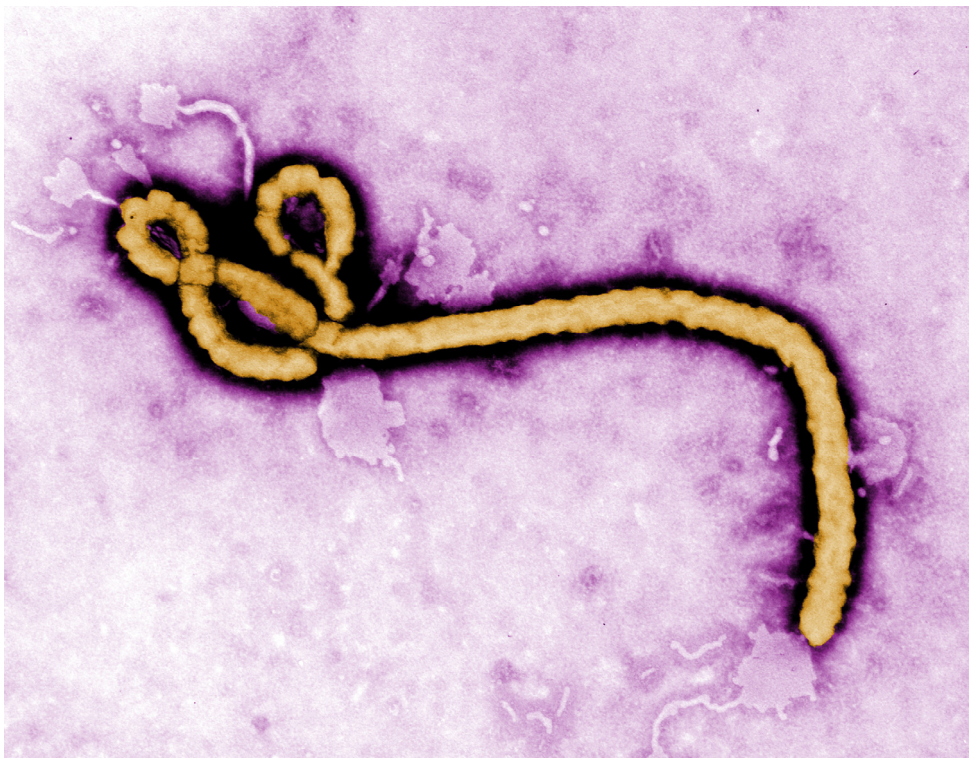
The SARS outbreak in 2003 had a considerable impact on us during the process of planning of the new facility in Malmö. At that time, SARS was a new disease, and it was initially not known how this syndrome spreads or how contagious it is. Many healthcare workers in Singapore, Canada, and Vietnam were infected via their patients, and there was significant spread between hospitalized patients and among people living in confined environments [48]. During the outbreak we had to care for and screen patients with suspected SARS in our out-of-date facility, and we to some extent perceived this as possibly unsafe for our staff. This situation demonstrates that it is necessary to be prepared for unknown diseases[48, 49]. SARS was later identified as a coronavirus infection with bats as the natural host[50], and by the end of the epidemic in 2003, over 8,000 cases and 774 deaths had been reported to the WHO[51].

Another coronavirus infection is MERS, which is transmitted to humans from camels and has given rise to epidemics in the Arab countries and caused spread in hospitals, including a large outbreak in South Korea[52]. Patients who have recently visited an area with an ongoing MERS outbreak and present with respiratory symptoms must be screened and isolated before being admitted to hospitals in other parts of the world if they have epidemiolocical riscfactors like contact with a verified case, camel contact or healthcare contact[53].

Seasonal influenza is a disease that is associated with often-underestimated mortality[54], and it causes a seasonal need for single-patient rooms in hospitals. At varying intervals, influenza A becomes pandemic (as in 1918, 1957, 1968, and 2009), which abruptly creates a huge need for isolation capacity and if necessary cohorting of patients.

Hemorrhagic fevers are often discussed when planning construction of advanced isolation units. The most recent example of such illness is the Ebola epidemic that occurred in West Africa in 2014–2015, cases of which were also noted in western Europe and in the United States, primarily among healthcare workers who were

transported home for treatment[55]. Ebolavirus belong to the group filovirus. Bats are also the natural host of Ebola[50].



Figur 2 Ebolavirus, colorized transmission electron microscopic (TEM) created by CDC microbiologist Frederick A. Murphy. Photo with pemission from CDC,USA.

1.4 Calicivirus

Calicivirus infections can also be considered emerging infections, because they have been increasing in recent years. The name calicivirus comes from the Latin word for cup (*calyx*), which refers to the appearance of the surface structures of the virus in an electron microscope.

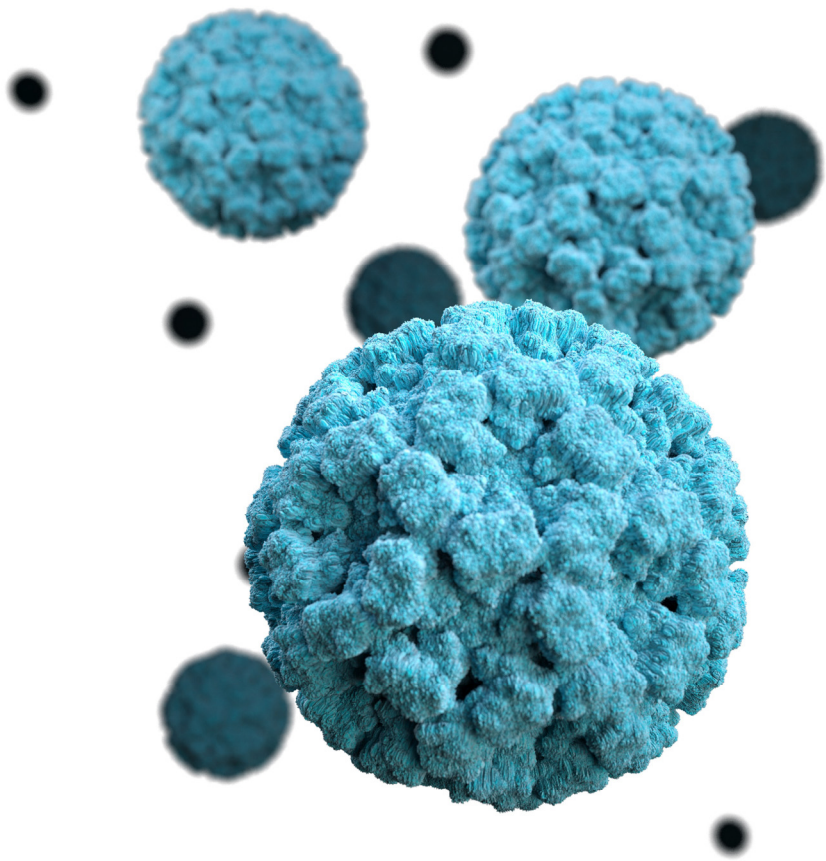
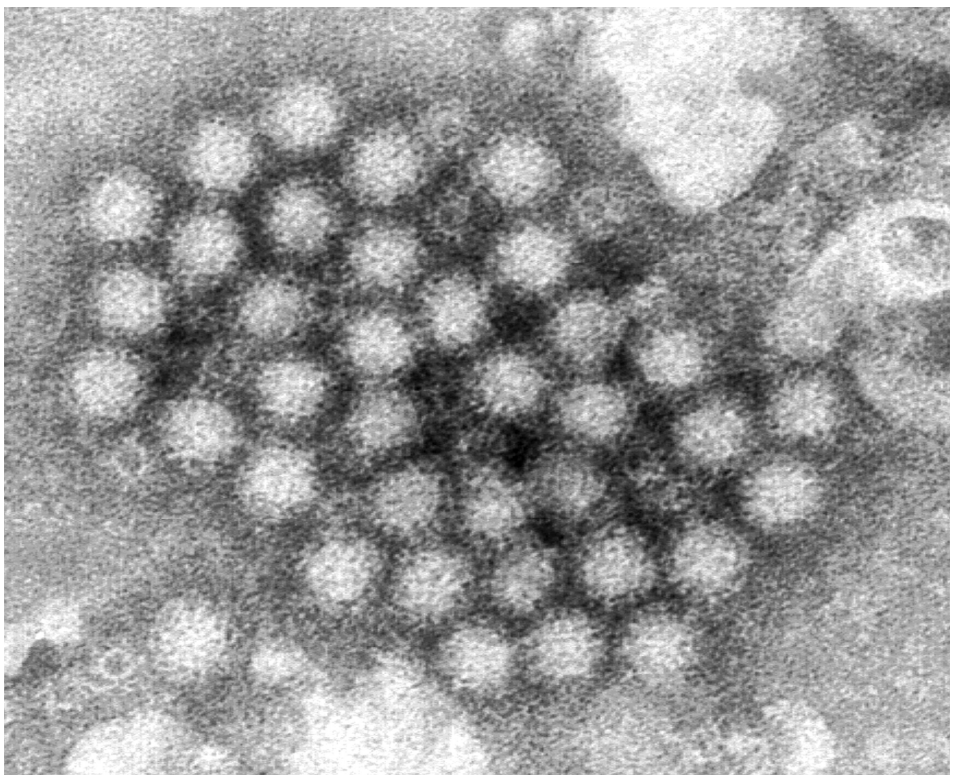


Figure 3. Human norovirus virions with the calyx like surface structures.
3D graphical representation by Alissa Eckert, with permission from CDC, USA

1.4.1 History

Winter vomiting disease has been recognized for many years and was first described in 1929[56]. In 1945, infectious material that had passed through a bacteria-excluding filter was given to volunteers; these subjects contracted the illness, and viral genesis was presumed even though the virus had not yet been isolated at that time[57].

In the United States in 1968, an outbreak of winter vomiting disease occurred among students and teachers in Norwalk, Ohio, and the cause was therefore named the Norwalk agent, which later contributed to the name norovirus. In 1972, volunteers who ingested purified fecal samples from the Norwalk outbreak displayed the same symptoms, and electron microscopy of their feces revealed small round viral particles[58]. However, electron microscopy was a cumbersome and very insensitive method at that time and remained the diagnostic method for many years[59].



Figur 4. Transmission electron microscopic image (TEM) revealing norovirus virions. Photo with permission from CDC,USA.

1.4.2 Virology

Caliciviruses belong to the family Caliciviridae, and they are non-enveloped, single-strand, positive-sense RNA viruses that are about 30 nm in diameter. Caliciviridae also comprises many animal pathogens, and the most prominent human caliciviruses are noroviruses and sapoviruses. The subgroup designated noroviruses includes five genogroups, three of which (designated I, II, and IV) infect humans and the remaining two infect cattle (III) and mice (V). Each genogroup is divided into several genotypes, which can be used to investigate outbreaks[60]. Sapoviruses in humans cause symptoms similar to those induced by noroviruses. All human caliciviruses were non-cultivable until recently[61], with the emergence of molecular techniques, and PCR is now the method that is commonly used for diagnosis of infections with these viruses[62].

1.4.3 Clinical features and epidemiology

Norovirus infection is one of the most common causes of gastroenteritis among adults,[63, 64] but can occur in all age groups. Typical symptoms are projectile vomiting and diarrhea. Norovirus infection is more common in the winter season, but it is also the most common cause of food-borne disease year around[63]. The incubation period is 24–48 hours, and symptoms usually last for 12–60 hours. The duration of norovirus infection is short and self-limiting in healthy individuals but can cause life-threatening disease in the elderly and in immunocompromised patients, mainly due to dehydration[65-66, 68-69]. Noroviruses can also cause chronic infection in immunocompromised individuals[69, 70], leading to the need for isolation management in re-hospitalized patients.

The attack rate during an outbreak is high due to marked diversity of genotypes, frequent mutations, and potentially short immunity[71]. About 20% of the population exhibit a special type of protection related to a host gene stop mutation in the fucosyl transferase 3 (*FUT3*) gene. Due to the aborted gene expression of this blood group glycan antigen present in the gastrointestinal tract, most noroviruses can not bind to their normal cellular receptor for virus attachment. [72, 73]. The susceptibility of an individual can be tested using a simple commercial test, although it should be noted that some norovirus genotypes are not dependent on intact *FUT3* gene expression[74].

1.4.4 Spread

Noroviruses are highly contagious and have a low infectious dose of 10–100 virus particles[75, 76]. During illness in the host, the virus is shed in large numbers of up to 10^{10} RNA copies/gram of feces[75, 77], and this shedding can continue for as long as 4–8 weeks[75]. Noroviruses are spread via the fecal–oral route, hand-to-hand contact, aerosols, and vomitus and diarrhea, as well as through contaminated food and water[78-80]. These stable viruses can persist on contaminated surfaces for long periods of time[80-82].

1.4.5 Disinfection and cleaning

Noroviruses are now a recurrent problem each year in our hospital, a situation that prompted us to perform the studies reported in Papers III and IV.

Viruses are either enveloped or non-enveloped. Enveloped viruses are easier to inactivate, because they are rendered non-infectious by destruction of the viral envelope, which is the location of the viral structures that can attach to receptors on the host cell. Enveloped viruses can be inactivated by alcohol and detergents, which disrupts lipid structures in the envelope. For noroviruses and other non-enveloped viruses, it is recommended to use bleach, hypochlorite, or hypochloric acid[83].

Despite repeated rounds of cleaning and disinfection, norovirus outbreaks occur in hospitals, nursing homes, schools and daycare centers, and restaurants, as well as on ships at sea, particularly cruise ships and ferries[84, 85]. Furthermore, norovirus infections cause huge problems in hospitals and nursing homes, because they lead to longer stays and postponed treatment for patients, closing of hospital wards, and sick leave among staff. Noroviruses are now a recurrent problem each year in our hospital, a situation that prompted us to perform the studies reported in Papers III and IV.

1.4.6 Surrogate markers for human noroviruses (HuNVs)

Attempts to propagate HuNVs in cell culture have been unsuccessful for almost 50 years, which has been a barrier in research concerning these important pathogens. The first successful culture system for HuNVs was described in 2016 in the journal *Science* by Ettayabi *et* al.[61]. One factor that contributed to their favorable accomplishment was that they used a model that to a large degree could recapitulate the environment in human intestinal epithelia. The system developed by Ettayabi

and colleagues remains highly complicated and requires human stem-cell-derived, non-transformed intestinal enteroid monolayers cultured in the presence of bile, and replication can be achieved only at low titers[61].

In contrast, murine norovirus (MNV) and feline calicivirus (FCV) are cultivable at high titers on murine and feline cell lines, respectively, and have been used for a number of years as surrogate markers for HuNV, for example, in inactivation studies of disinfectants[86-90]. FCV is a respiratory virus that causes significant morbidity in cats. In contrast, like HuNV, MNV infects its host and is shed via the gastrointestinal tract. Many inactivation studies have focused on FCV, although the trend has been changing towards MNV, because the latter has the same transmission route and is structurally more similar to HuNV[91].

1.4.7 PCR

Virus culture in cells is time and labor consuming, and thus in practice has been replaced by polymerase chain reaction (PCR) as a diagnostic method for pathogen detection. PCR is also widely used for the numerous viruses that can be grown in cell culture. In research concerning hospital hygiene, the drawbacks of PCR are that it only detects nucleic acid and does not differentiate between inactivated and viable virus.

1.5 The history of hospital buildings designed to prevent infections

"*The times they are a changing*" Bob Dylan[92].

In the pre-antibiotic era, buildings for care of patients were designed to support good hygiene in order to prevent the deadly threats posed by communicable diseases, and this was done even before bacteria and viruses were discovered. Hospitals were constructed in pavilions with a great deal of space between buildings and large volums of air inside and had natural ventilation. Infectious diseases or epidemic hospitals were often located at the edges or even outside of hospital areas, and in many of these facilities the entrances to the patient rooms were from the outside and via anterooms.

There are some early examples of separating patients with contagious diseases. Leprosarums were common during the middle ages. In the 15th century, the authorities in Venice, Italy, confined plague victims in lazarettos such as Lazaretto Vecchio on the small island of San Lazaretto Nuovo to avoid spread of the disease[93].

Earlier during the plague epidemic of 1377, the Great Council in Ragusa (now Dubrovnik, Croatia) decreed that foreign travelers should be isolated for 30 days before being allowed to enter the city in order to prevent the spread of the plague, and this regulation was called Trentino (from *trenta*, which means 30 in Italian). Equivalent decrees were later introduced in other European cities but were changed to comprise 40 days and hence were named *quarantaine*, which means approximately 40 in French[94].

Figur 5 Copper engraving: Doctor Schnabel a plague doctor in Rome ca 1656. Photo Wikipedia

In England, the segregation of people with smallpox and fevers was formalized in the early 19th century when fever hospitals were established[93, 94].

In the early 20th century, our hospital in Malmö had special wards for patients with scarlet fever and these patients were placed in quarantine for weeks. Today, patients with this disease are treated at home with a 10-day course of antibiotics.

After World War II, when antibiotics had been discovered the hospital buildings were centralized and constructed to enable more industrial production and often

We are presently facing a post-antibiotic era and in addition have already experienced emerging infections such as SARS.
To meet this challenge, we have to revive some old concepts from the pre-antibiotic era and combine them with new techniques to develop novel strategies that can help prepare us for a future with more serious threats from infections.

organized in central hospital complexes with rational flows of patients, and infections were not considered as important as before.

We are presently facing a post-antibiotic era and in addition have already experienced emerging infections such as SARS. To meet this challenge, we have to revive some old concepts from the pre-antibiotic era and combine them with new techniques to develop novel strategies that can help prepare us for a future with more serious threats from infections.

1.6 New buildings

"*We shape our buildings and afterwards our buildings shape us"* Winston Churchill[95].

A great many new hospitals will be built around the world in the near future to replace the countless facilities that were erected before or during the 1970s and are now outdated in many aspects [96]. The demands on modern hospital buildings have also changed with introduction of new techniques, and there are increasing quality requirements that must be fulfilled to meet the needs of both the patients and the staff, for example, in terms of more single-patient rooms and more efficient work spaces[97]. It can be noted that there is a trend towards shorter length of stay and use of out-patient treatment in association with many surgical procedures and other treatments, but at the same time there is also an increasing need for new hospital facilities, because the population is getting older.

In conclusion, the decisions that we make today with regard to the design of new hospital facilities will have a long-term impact on healthcare, and this offers us an unique opportunity to shape future hospital care.

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1.7 Evidence-based design

"*Architecture is a non-medical measure that can contribute to medical outcomes*" Stefan Lundin[98].

Evidence-based design (EBD) is a relatively new field of hospital planning that aims to make it possible to evaluate hospital design in the same way as medical procedures, devices, and drugs are assessed. In addition, EBD borrows terminology and ideas from disciplines such as environmental psychology, neurosciences, and immunology, and it is also related to "healing architecture", a concept implying that design that takes into consideration of aspects such as color, light, and privacy can support the process of healing.

One of the first examples of EBD, and in a way the beginning of this field, is illustrated by an article by Roger Ulrich published in *Science* in 1984[99]. Ulrich studied patients who had undergone a cholecystectomy and found that those who could see trees from the window in their hospital room had a shorter length of stay and required less analgesics compared to those who could only see a brick wall. Other examples of areas in which EBD is used include evaluation of the positive influence of daylight [100], and single-bed rooms and the negative effects of noise on patients. EBD can also be applied to the working conditions of hospital staff, for instance to assess the impact of design on overview, orientation, and spontaneous meetings with colleagues and moving of patients and staff [97], as well as factors such as the importance of daylight and the negative influence of noise[101, 102]. The number and accessibility of hand-washing facilities and alcohol dispensers can affect the frequency of hand washing and hence also the frequency of nosocomial infections[42].

In conclusion, as in the field of medicine, more evidence-based knowledge is needed in the design of hospitals. There is presently a trend away from the more industrial view on hospitals that was prevalent in the 1970s, with the focus now returning to the knowledge that the environment in which patients are treated constitutes a part

of the healing process. Again—old concepts are being reintroduced. Notably, the architects who planned the Department of Infectious Diseases in Malmö were inspired by EBD, for example, with regard to the need for daylight and windows with a pleasant view in hospital rooms.

...the environment in which patients are treated constitutes a part of the healing process

1.8 Single-patient rooms

Most people in Sweden today would not accept being randomly booked in a hotel to share a room with one or more other individuals with whom they are not acquainted. So a question for the future is whether people who are ill and admitted to a hospital will accept this and the risk of being infected or colonized with viruses and bacteria spread from other patients that is associated with sharing a room.

A recent review article by Stiller et al.[103] demonstrated that single-patient rooms are beneficial for infection control and are useful parts of a multifaceted strategy for reducing healthcare-associated colonization of patients and infections. Stiller and coworkers found that six out of nine studies that met the inclusion criteria showed a significant (i.e. nearly 50%) reduction in HAIs. Most of the investigations included in that review were performed in intensive care units.

The trend in construction of modern hospitals is increasingly favoring single-patient rooms, especially in the United States. Additional advantages of single rooms include the following: less moving of patients, which improves patient safety[104]; enhanced patient privacy and confidentiality[105, 106]; better communication with patients and family members and thus improved social support[107]. A critical issue for the future is whether we should only build single-patient rooms.

1.9 Conventional cleaning and disinfection

1.9.1 Background

Cleaning of healthcare facilities is important, not only for the general well-being of patients but also to reduce the microbiological load in the patients' environment and thereby indirectly diminish HAIs and the spread of resistant bacteria[108,109]. It is essential that facilities and surface materials therein are designed to enhance cleaning[46, 47, 110]. Good cleaning and effective ventilation will reduce dust that can contain bacteria, fungi, endospores, and viruses[111].

Another critical aspect in the planning of cleaning is to know where in a patient room the microbial contamination is highest. The most contaminated surfaces are near the patient areas and areas frequently touched by the patient (high touch surfaces), examples of which are the bed, the bed table, and remote controls[112-114]. In the patient bathroom, there can also be extensive contamination of faucets, toilet paper holders, and soap dispensers[115]. The floor is contaminated by deposited shed skin flakes and by dust and dirt from shoes, but the walls are usually less contaminated[116]. Some individuals are heavy spreaders, such as patients or staff with skin infections or vomiting or diarrhea, which will further contaminate surfaces[117].

The hands of staff members should also be mentioned[43]. It is important to decontaminate computers, ventilator displays, phones, and infusion pumps that are frequently touched by staff[114, 118, 119]. Moreover, staff wear disposable gloves to protect themselves, and touching all surfaces, contaminated or not, without changing the gloves will transfer infectious material[118].

To maintain adequate cleaning, this process should be standardized and certified, and include written protocols that require strict adherence[120]. Education of the cleaning staff is also very important. Cleaning that is done incorrectly, in the wrong order, or using worn out equipment can actually exacerbate or spread the contamination [121, 122]. It can also be noted that the difference between cleaning and disinfection in routine practice is relatively small[123-125]. Disinfection causes more abrasion of surfaces, is more harmful for the staff to handle, and should only be used when needed to combat certain infectious agents[125].

1.9.2 Evaluation of cleaning

The effectiveness of cleaning can be evaluated in many ways[111]:

- Visual assessment. Visible contamination (e.g. with blood or organic material) should always be removed immediately by spot disinfection.
- Measurement of dust levels.
- Measurement of adenosine triphosphate (ATP) determines metabolic activity that can come from microbes but also from other biological material such as skin flakes. Although this method is still under debate[122], it can be used to provide feedback to the cleaning staff[115].
- Use of UV light to measure fluorescence on surfaces that have been marked with fluorescent dye.This is a fast and simple method that can also be used for training of staff[126].
- Numerous culture techniques are used. Dip slides and agar contact plates are two common culture methods. Another technique is to rub sterile swabs are over a defined area and then shake them in culture medium.

Cleaning and hygiene in hospitals have been regarded as crucial aspects and even as a virtue since the days of Florence Nightingale. Sadly, the quality of cleaning has deteriorated in many hospitals during the last decades due to financial cuts. Furthermore, to some extent there has been outsourcing of cleaning without observing sufficient quality control or considering that surfaces play an important role in the transmission of pathogens, a topic that has received less attention in recent years. However, interest in this issue is once again increasing due to strong reactions from patients and the media, and because of the spread of resistant bacteria and hospital-acquired infections.

1.9.3 Cleaning and disinfection at Skåne University Hospital

Cleaning is performed in a variety of ways at different hospitals, and in this section Skåne University Hospital (SUS) in Malmö is used as an example of how this task can be carried out. In the wards at SUS, “conventional” cleaning is performed daily in all patient rooms by the cleaning staff, who use microfiber products and water to remove all visible dust and dirt. Spot disinfection with alcohol is performed immediately by the healthcare staff of visible contamination of blood and organic material. The surfaces that are close to and frequently touched by the patient (e.g., the bed, the bed table, and remote controls) are cleaned daily with alcohol and surfactants by the healthcare staff. A novel alternative that is tried is to use ready-made hydrogen peroxide wipes in this areas.

Stricter procedures are applied for patients with a known transmissible infection like norovirus; in such cases, Virkon ®(a disinfectant based on hypochloric acid) is used for daily disinfection and for terminal disinfection of all surfaces. Furthermore, in certain cases, it is necessary to use disinfectants rather than surfactants (see below). For example, when a patient has a *C. difficile* infection, chlorine is used for terminal disinfection. When a patient is a suspected or verified carrier of resistant bacteria (e.g., MRSA, VRE, or *Acinetobacter*), Virkon® is used on the floor and alcohol and surfactants on other surfaces, and the cleaning/disinfection is done daily and for terminal disinfection.

1.9.4 Why is conventional cleaning and disinfection not always adequate?

It is becoming increasingly evident that contamination of surfaces plays an important role in transmission of many key pathogens in healthcare-associated infections. Examples of such microorganisms are MRSA, VRE, *C. difficile*, and *Acinetobacter*, which share these traits[127, 128]: they can survive for long periods on surfaces, and they can spread directly to patients or via the hands of staff or other patients.

Well-informed patients should ask what diagnosis the previous patient occupying a particular room had and reject that room if the earlier occupant was infected with *C. difficile* or norovirus, or was a carrier of resistant bacteria.
This is an overwhelming argument for caregivers to provide safe and clean hospital rooms for newly admitted patients.

There is often residual contamination of rooms with bacteria, spores, or viruses from patients even after repeated rounds of conventional cleaning or after manual disinfection[128-130]. The contamination remaining after manual cleaning can also be shown using ATP and fluorescence markers[131]. In short, ATP and fluore-scence markers indicate the presence of organic material and thus measure the quality of cleaning but not the growth of microorganisms.

If a patient is assigned to a room in which the previous patient was a carrier of bacteria such as MRSA, VRE, *Acinetoobacter baumannii*, *Pseudomonas aeruginosa*, or *C. difficile*, the risk of acquiring the same disease or carriage as the previous patient is increased by a factor of ≥ 2. This was clearly demonstrated in a meta-analysis published in the *Journal of Hospital Infection* in 2015[67, 130, 132].

Well-informed patients that are aware of this risk should ask what diagnosis the previous patient occupying a particular room had and reject that room if the earlier occupant was infected with *C. difficile* or norovirus, or was a carrier of resistant bacteria. This is an overwhelming argument for caregivers to provide safe and clean hospital rooms for newly admitted patients.

1.10 No-touch decontamination (NTD)

1.10.1 History

A variant of NTD called "formalin smoking" has been used for over a hundred years, and this approach was reported in a paper published in 1901 that described how a "sick room" was treated with gaseous formaldehyde[133]. Due to the toxicity of this method, in the 1960s it was replaced with aerosolized quarterly ammonium compounds, phenolic, or UV light to eliminate bacterial load[134, 135]. At the end of the 1970s, interest in chemicals for this purpose was diminishing due to the toxicity and to the perception that infections were under control. Surfaces and air were considered less important in the spread of infections.

1.10.2 When can NTD be considered?

When conventional cleaning is not an adequate approach, NTD can be the solution. In contrast to manual cleaning, which is highly dependent on who performs the cleaning and is very difficult to standardize, NTD represents a general method of decontamination that is automated and standardized[136, 137]. Nevertheless, it is always necessary to carry out manual cleaning of a room before conducting NTD in order to eliminate visible dust/dirt and thereby reduce the organic load that can otherwise inactivate the disinfectant[136]. NTD cannot be regarded as the sole method of decontamination/cleaning but rather as a complement to manual cleaning. NTD has been frequently used in the pharmaceutical and food industries, where demands on hygiene are high, and it has also been applied in research laboratories, particularly those using experimental animals.

The mentioned methods are further examples of techniques from the pre-antibiotic era that are being modernized and reused!

The more susceptible the patients are to infections, the lower the infectious dose is, the more dangerous the pathogens are and the more likely the pathogens are to survive on surfaces, all this supports the need for NTD. Examples of pathogens that are shed in high numbers and have a low infectious dose, and that can survive on surfaces for considerable periods of time are *C*. difficile and noroviruses [76, 77, 128, 138]. The pathogens *Acinetobacter* and VRE can also show prolonged survival on surfaces, and in addition are difficult to eliminate from hospital facilities[128].

For economic and logistic reasons, NTD is not a realistic strategy for daily cleaning of patient rooms. However, NTD is suitable for terminal room disinfection, because patients are not allowed to be in the rooms during that process.

1.10.3 NTD systems

There are three main systems that are used for NTD: UV light, ozone, and hydrogen peroxide.

UV light

UV light has been used for many years for disinfection of surfaces, instruments, and air[136, 139], as well as for decontamination in the food industry. The mode of action of UV light is to kill microorganisms by breaking the molecular bonds in DNA[140]. Two systems are chiefly in use for NTD: ultraviolet light wavelength C (UVC) with a wavelength of 200–270 nm, and pulsed xenon radiation with a broader wavelength of 200–320 nm.

UV light has an inherent problem with "shadow effects", because it travels in straight lines and is less effective when out of sight of the decontamination device[136]. In an attempt to overcome this obstacle, some systems are constructed as mobile units that are moved by a computer. The efficacy also depends on the distance from the UV device, exposure time, organic load, and placement and intensity of the lamp, as well as the shape of the room and types of surface materials present and how reflexive the surfaces of the walls are[140]. UV light achieves dose-dependent killing, and the doses required to eliminate bacteria and spores vary. It appears that the dose needed to eradicate *C.* difficile is twice as high as the dose required to kill common vegetative bacteria[140].

UVC is the most widely used UV method, and it is considered harmless and does not necessitate sealing of the room to be treated. Moreover, UCV is relatively fast, and the time required depends on the organism(s) being targeted, the size of the room, and whether multiple cycles have to be performed in different parts of the room. The total time varies from 10 to 70 min in different studies. The efficacy of the decontamination varies between 2 and 4 log reduction of *Acinetobacter*, VRE, MRSA, and *C. difficile*, as summarized by Weber et al. in a review article presented in the *American Journal of Infection Control*[140].

A pulsed xenon ultraviolet (PX-UV) light device uses short pulses of broad-spectrum UV light and represents further development of the UVC method to make it faster. It only takes 10–15 min to perform PX-UV treatment, and the UV equipment can be systematically placed in different parts of a patient room during the decontamination to overcome the shadow effect.

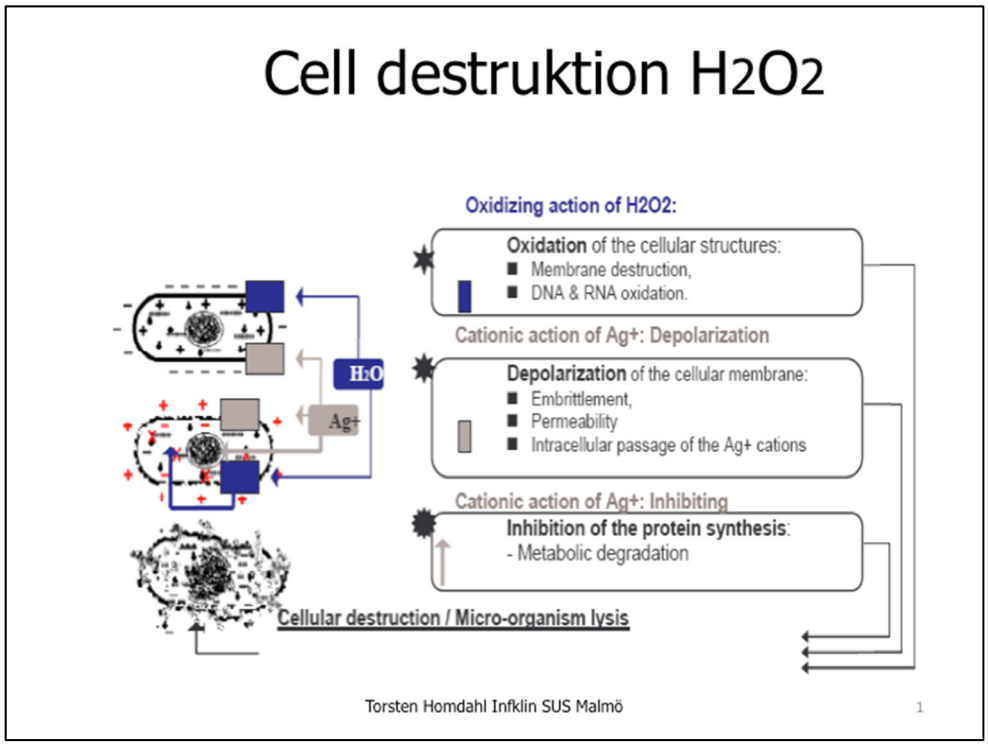
Ozone

Ozone gas can be used to eradicate bacteria and viruses from surfaces[141, 142]. This strategy is employed in the food industry and also as a means of eliminating odor in cars and aircraft by decontamination of microorganisms[142]. Unfortunately, ozone can be harmful to human health and is toxic at higher concentrations. Therefore, when ozone is used in healthcare settings, the rooms to be treated have to be sealed off, and leakage must be measured. The typical odor of ozone that can be perceived directly after use disappears relatively quickly. Another important aspect is that ozone has a corrosive effect, and further investigation is needed to determine compatibility with medical equipment.

Ozone causes > 3-log inactivation of common hospital bacteria such as *C. difficile*, *S. aureus* (including MRSA), *E. faecalis*, *E. coli*, and *A. baumanii*[142]. The efficacy of ozone is only superficial, as exemplified by an experiment we conducted which showed the following[143]: in a patient room, the impact of ozone was inadequate on 10^6-log Tyvek-pouched Geobacillus stearothermophilus spores but was highly effective on such spores spread out in a monolayer.

Hydrogen peroxide

Hydrogen peroxide acts as oxidant against bacteria and viruses by producing hydroxyl free radicals that attack proteins, lipids, and nucleic acids. Inasmuch as the mode of action of hydrogen peroxide is so complex and targets many parts of the cell (e.g., cell membranes and protein synthesis), there is little risk for development of resistance[144].



Figur 6 The mode of action of hydrogen peroxide is complex and targets many parts of the cell of the microorganisms. Figure with permission of Mats Walder

Hydrogen peroxide has broad antimicrobial activity with efficacy against bacteria, viruses, fungi[145], bacterial and fungal spores[145], and *Mycobacterium tuberculosis*[146]. The antibacterial effect can be exploited in hospitals to address the problem with cells and spores of pathogens such as *MRSA, VRE*, *A. baumanii* and *C.difficile*[45, 147-149]. The virucidal effect is exerted on both enveloped and non-enveloped viruses, and on respiratory and enteric viruses[150] (e.g., poliovirus, rotavirus, and adenovirus), as well as on the feline and murine noroviruses[87, 151].

Hydrogen peroxide is environmentally friendly, because it is degraded to water and oxygen. This is an important aspect considering that many other disinfectants (e.g. glutaraldehyde, phenolic, and hypochlorite) have a negative impact on the environment. Hydrogen peroxide has no reported corrosive or negative effects on medical devices, which gives the possibility to put the devices in the room that is to be treated to get them decontaminated. Fabrics (e.g., bed linen, furniture upholstery, or curtains) can remain in a patient room during decontamination, although the presence of large amounts of fabric can make it necessary to use more hydrogen peroxide to maintain a high concentration.

Hydrogen peroxide is toxic to humans, and therefore it is necessary to seal doors with tape and turn off or cover the inlets of the ventilation system in a room during the decontamination process. It is safe to enter the treated room again when the level of hydrogen peroxide is < 1 ppm[152], or wearing a mask in case of emergency. The treatment must be performed by specially trained staff. It is also important to emphasize that manual cleaning must always be done before the decontamination to remove visible dirt and dust, because organic material can to some degree suppress the effect of hydrogen peroxide[150].

In addition to being used as a local disinfectant, hydrogen peroxide can be introduced chiefly by two different systems of no-touch distribution, one based on hydrogen peroxide vapor (HPV) and the other using aerosolized hydrogen peroxide (aHP). Below, no-touch hydrogen peroxide decontamination is exemplified using information from Paper II, which gives a representative picture of the main principles of the two systems. Both systems produce Hydrogen peroxide from mobile generators. The HPV system uses 30% hydrogen peroxide solution, which is distributed as a heat-generated vapor; the term vapor is used exclusively to indicate a droplet size of < 5 µm. The aHP system uses 5–6% hydrogen peroxide solution, which is distributed as a pressure-generated aerosol with a droplet size of 8–12 µm. In the aHP system described in Paper II, hydrogen peroxide is also combined with silver and phosphoric acid to stabilize the droplets. Some other aHP systems combine hydrogen peroxide with peracetic acid, which might add a synergistic effect. In general, the HPV systems achieve higher concentrations (ppm levels) and a smaller droplet size.

After studying the literature and investigating the two hydrogen peroxide systems, we took field trips to two hospitals in the United Kingdom and one in Denmark to observe use of the devices in clinical practice, as described below.

In the United Kingdom, we studied HPV at visiting Royal Marsden and Guy's and St. Thomas's Hospitals. Those facilities began using HPV to address the spread of *C. difficile* 027, and the efforts to combat the bacteria were funded by the National Health Services and HPV was chosen as method for that. At Royal Marsden Hospital, the HPV equipment used belonged to Bioquell and was run by Biquell staff. First, all rooms were treated with HPV after discharge of *C. difficile*-positive patients. Thereafter, other rooms that had harbored patients with resistant bacteria were also HPV treated. Finally, if there was time, additional rooms were treated. Thus, over a period of time, all rooms were treated with HPV. At Guy's and St. Thomas's, the HPV devices used were bought by the hospital and run by specially educated hospital cleaning staff, who were very enthusiastic and regarded it a way of creating a career. In about the same manner as at Royal Marsden, all rooms at Guy's St. and Thomas's Hospital were treated over a longer period, and rooms that had housed patients with *C. difficile* or resistant bacteria were treated very rapidly

by a rapid resonse team of cleaners to diminish the the time that the rooms had to be empty.

In Denmark, we visited Herlev Hospital where an aHP system from Glosair had been introduced due to an outbreak of *C. difficile* 027. The device in use was bought by the hospital, and members of the cleaning staff received training in how to handle the system themselves. Notably, equivalent to our observations in the United Kingdom, we found that the cleaning staff in Denmark also felt that they had become very dedicated to achieving correct implementation of the aHP system and considered it a career development .

In conclusion, at all three of the hospitals we visited, the hydrogen peroxide systems that were used were well accepted by the staff, and there did not seem to be much concern about the toxicity.

1.10.4 Which NTD system should be used?

"The answer is blowin in the wind" Bob Dylan[153]

Conventional cleaning must be done before using any of the mentioned NTD systems. Visible dirt and dust must be removed, because organic material reduces the efficacy of these devices[136]. It should be noted that each type of NTD system has drawbacks, as listed below.

Ozone is toxic to humans and may have corrosive effects on medical equipment. Moreover, ozone has only a superficial effect and thus does not seem to be an acceptable alternative at present.

UV light is expensive to buy but entails a low operating cost. It is not toxic and easy to use, and does not require sealing of doors or monitoring for toxicity. Decontamination with UV light is fast, especially with PX-UV devices. However, UV light systems have lower efficacy compared to hydrogen peroxide systems and also include a risk of uneven distribution in the rooms. UV light might be attractive under circumstances when easy handling and speed are important and residual contamination can be accepted.

Compared to UV light approaches, the hydrogen peroxide systems are more efficient, but toxicity makes it necessary to seal the treated rooms and turn off/close the ventilation, and it takes longer to perform the decontamination. Compared to an aHP system, an HPV device is more expensive to buy but functions somewhat faster because it has an aeration unit. More studies have evaluated the use of HPV than aHP, and in most cases the results have shown higher efficacy for HPV in eradicating bacteria and spores.

The pros and cons of different NTD systems are summarized in a review article recently presented by Weber et al.[139]. There is also a discussion regarding types of study design such as the following:

1) *In vitro* investigations exploring elimination of relevant microorganisms.

2) Decontamination studies in patient rooms with relevant pathogens on carriers.

3) Evaluations demonstrating elimination of naturally contaminated environmental surfaces in patient rooms.

4) Before and after studies showing a reduction in HAI incidence after introduction of an NTD system.

5) Crossover studies with multiple sites or crossover points.

6) Randomized clinical trials.

There are very few investigations of types 5 and 6, and more head-to-head studies are needed including studies that are of type 2. There is also a lack of health economic studies of NTD.

In conclusion, there is no single answer to the question of which system should be used, and therefore more research is needed in this area.

1.10.5 Summary and comparison of different NTD systems

Table 1 .Comparison of different NTD systems

NTD system	HPV	aHP	Ozone	UVC	PX-UV
Efficacy, common hospital bacteria *in vitro*	6-log reduction	4-log reduction	3-log reduction	2–4-log reduction	2–4-log reduction
Depth of cleaning	+++	++	+	+	+
Running time	2–3 h	2–3 h	50 min	10–70 min	10–15 min
Toxicity to humans	Toxic, rooms must be sealed 1 ppm limit	Toxic, rooms must be sealed 1 ppm	Toxic, rooms must be sealed 0.1 ppm	None	None
Corrosive effects	None	None	Yes	None	None
Purchase cost	++	+	?	++++	+++
Running cost	Low	Low	Low	Low (Bulbs)	Low (Bulbs)
Additional disadvantages			Odor during use, Need of high humidity	Shadow effects, uneven distribution	Shadow effects, uneven distribution

In conclusion, there is no single answer to the question of which system should be used, and therefore more research is needed in this area.

2 Aims

The overall objective of the present research was to apply hospital design and decontamination methods to find techniques that can reduce and prevent the risk of spreading of resistant bacteria and infections between patients, to hospital staff, and to society in general.

The specific aims were as follows:

-- To describe the experience of planning a new facility for infectious diseases in Malmö, Sweden, and to discuss underlying theories related to infection prevention and evidence-based design.

-- To compare the efficacy of two different hydrogen peroxide systems (HPV and aHP) in eradicating biological indicators (BIs) in a full-scale model patient room.

-- To determine whether HPV can be used to decontaminate surfaces from caliciviruses in a patient room.

-- To ascertain whether inactivation of noroviruses with hydrogen peroxide is reflected by quantitative PCR (qPCR) levels compared to viability.

3 Methods

3.1 Macro perspective

The scientific methods employed in the present research differ between the first study (Paper I) and the other three traditional experimental studies (Papers II–IV).

Paper I describes our investigation of a more complex process in which approaches other than, for example, a randomized clinical trial had to be applied to obtain a meaningful evidence base, noting that such studies are more common in architecture than in medicine. We conducted a retrospective, theory-generating case study.

Methods used were: In an attempt to predict the future of infectious diseases by looking back to determine how much had happened during the previous 25 years, and subsequently presuming that there will be equivalent degrees of change and new diseases in the coming 25 years. In this investigation, we explored trends in antibiotic resistance, demography, and climate, and we performed literature reviews including evidence-based design. Furthermore, we held focus groups including all categories of staff, and we made field trips to infectious diseases facilities in the United Kingdom, Denmark, and Norway, as well as most such facilities in Sweden. We used a mock-up patient room (Fig. 7), which was visited by 120 members of the ID hospital staff, who answered prepared questions and freely made comments and suggestions. External expertise was consulted, and we also took into consideration healthcare architecture design precedents from the pre-antibiotic era that might be relevant in the post-antibiotic era.

Figur 7 The Mock up inside a former ship building hall in Malmö harbour. Photo: Torsten Holmdahl

In the program and during the planning we tested suggestions and ideas against three main principles that we designated as follows:(1) far away yet nearby, (2) flexibility, and (3) defined links, and these principles now constitute established aspects in further evaluations:

1. Far away yet nearby

Traditionally, isolation wards were located as free-standing units in the outer areas or even outside of the hospital grounds. However, modern standards for patients with infectious diseases require proximity to pivotal major hospital facilities such as the ICU, radiology, surgery, and emergency medicine departments. Therefore, instead of placing an isolation unit at a greater distance from the main building, it should be established within that facility, if it is a modern building in which the impact of an isolation ward can be ameliorated through technical solutions such as separate and advanced ventilation, isolated elevators, and exterior entrances to patient rooms. Based on this principle, we evaluated whether we could were successful in combining the earlier physical distance with modern demands of proximity.

2. Flexibility

This principle of flexibility challenges the following: how well the patient rooms can be used both for every day care and in the same format for isolation of high-risk patients; whether the facility allows higher occupancy (two patients per room) during seasonal variation situations and outbreaks.

3. Defined links

This principle implies that it should be possible to separate the flow or circulation of patients with regard to those who do and those who do not have contagious diseases.

3.2 Micro perspective

3.2.1 Settings for decontamination studies

We used full-scale patient rooms in two of the studies (Papers II and III), whereas a test chamber was employed in the fourth investigation (Paper IV). The room described in Paper II was built as a full-scale mock up of a patient room in the planning of a new infectious diseases facility. This test room had an area of 136 m^3 and was divided into four sub-rooms: two air locks (one outer and one inner), a main room, and a bathroom.

The third study (Paper III) was performed in the old infectious diseases facility in Malmö, which had been decommissioned but was otherwise intact after the move to the new facility. The test room used was a single-bed patient room with an en suite bathroom and a total area of 52 m^3. An equivalent room was used for unexposed controls. In two of the studies (Papers II and III), the external doors were sealed using adhesive tape due to the toxicity of hydrogen peroxide, and leakage was monitored periodically during the tests by use of a handheld sensor. In both these investigations, chairs and bed mattresses with fabric upholstery/covering were left in the room during treatment. The ward was equipped with a dedicated air-handling system leading to the outside of the building, which was used to facilitate removal of hydrogen peroxide at the end of the tests.

In the fourth study (Paper IV), we used a permanently installed 16-m^3 decontamination chamber connected to a Bioquell Q10 Suite to generate HPV. This system is used to decontaminate products before they are taken into an experimental animal laboratory.

3.2.2 Biological indicators (BIs)

In the second study (Paper II), the microbiological efficacy of the two systems was tested using 6-log Tyvek-pouched *G. stearothermophilus spores* as BIs (Apex laboratories). To test the efficacy and distribution of the systems, the BIs were placed in the different test rooms in high and low corner locations, as well as in several challenging locations such as inside cupboards and drawers. After exposure to either HPV or aHP, the BIs were transferred into tryptone soya broth, incubated at 55 °C for 7 days, and read according to the manufacturers instructions. In the third and fourth studies (Papers III and IV), BIs were also used in the same manner and in duplicate adjacent to each virus test plate as a control for HPV efficacy and distribution.

3.2.3 HPV decontamination

In the second study (Paper II), we used one Bioquell Q10 suite according to the recommendations of the manufacturer.

Figur 8. The Bioquell Q 10 HPV device. Photo provided by Bioquell.

The HPV generator (Q10) was placed in the center of the main room; the R10 (aeration unit) was placed in the doorway of the main room airlock; an oscillating pedestal fan was placed in the doorway of the bathroom and in the outer air lock; and the control pedestal was placed outside the door of the main room. Hydrogen peroxide concentration, temperature, and relative humidity in the room were monitored by the Q10, and the readings were recorded every 5 min during the injection phases and regularly during aeration (i.e., the removal of HPV) In each of the three tests, 900 ml of hydrogen peroxide was injected with 30-min dwell time, which equates to approximately 6.6 g/m^3. Aeration was assisted using the air handling system. The test was considered concluded when the readings from the handheld sensor were ≤ 1 ppm in the air lock and ≤ 2 ppm at any point in the patient room. (The health and safety limit for hydrogen peroxide exposure in Sweden is 1 ppm for a working day and 2 ppm for a period of 15 min[152].)

Inasmuch as HPV was found to be superior to aHP in the head-to-head study (Paper II), only HPV was used in the two subsequent investigations (Papers III and IV). The HPV was applied in the same way as described in Paper II, adjusting the system to the room size according to the manufacturer's instructions.

3.2.4 aHP decontamination (Paper II)

Two aHP generators (Run by Bakterifritt, devices same as Sterinis or Glosair) (Fig. 9) were used due to the size of the room in compliance with the manufacturer's recommendations. The generators were placed in the center of the main room. Inside the enclosure, the concentration of hydrogen peroxide was measured using a Draeger sensor (Polytron 7000). For each of the three tests, three back-to-back injections of 6 ml/m^3 hydrogen peroxide were performed. Aeration was assisted using the air-handling system. The test was considered ended at the same ppm levels as described above.

Figur 9. Two aHP devices (Run by Bakterifritt) in action in the mock up during study 2. Photo Torsten Holmdahl

3.2.5 Viruses and cells (Papers III and IV)

FCV (feline calicivirus (FCV; strain 2280 (ATCC VR-2057)) and a feline permissive fetal cell line (FCWF) were used and cultured in media in the third study (Paper III), and MNV (murine norovirus strain Berlin/06/06/DE S99) and a corresponding murine permissive RAW 264.7 cell line were used and cultured in media in the third and fourth studies (Papers III and IV). All plastic material used for cell culture (6-, 24 and 96-well plates and flasks) was from Corning Life Sciences (UK).

In the fourth study (Paper IV), the two human strains that were used, one HuNV genogroup I (GI) and the other HuNV genogroup II (GII), originated from routine clinical feces samples provided by the Department of Microbiology, Skåne University Hospital (SUS), Lund. Clarified 10% feces samples in PBS were prepared by centrifugation at 18,000 x G and stored at –20 °C.

Virus stocks

FCV. Three 25-cm^2 bottles of the FCWF cells were grown to 80–90% confluence. Next, the medium was removed, and 200 µL of virus inoculum was added to 1 mL of the cell medium and incubated for 2 h at 37 °C in 5% CO_2. The inoculum was then removed, and fresh medium was added. All supernatant material harvested up to 48 h was clarified by centrifugation at 1,200 rpm for 5 min and further by ultracentrifugation at 39,000 x g for 1 h to concentrate the viral stock. The stock solution was aliquoted and stored at –70 °C.

MNV. Three 25-cm^2 bottles of the RAW 264.7 cells were grown to 80–90% confluence. The medium was removed, and 500 µL of virus inoculum was placed on the naked cells, which were subsequently incubated for 1 h at 37 °C in 5% CO_2. The inoculum was then removed, and fresh medium was added. After 5 days, when a complete cytopathogenic effect (CPE) was observed, the medium was harvested. The cells were removed by centrifugation at 1,200 rpm for 5 min, and the clarified supernatant was aliquoted and stored at –70 °C.

3.2.6 Preparation of contaminated plastic surfaces for subsequent exposure to HPV (Papers III and IV)

Virus stocks and/or human clinical isolates and a mixture of 50% each of the HuNV and MNV were thinly spread in triplicate around the centers of three 35-mm wells in six-well plates and allowed to dry at room temperature in a hood. When completely dry after 2 h, the plates were stored at –70 °C until used. On the day of an experiment, the plates were placed in the test rooms as described below.

3.2.7 Quantification of replicating viruses

Virus viability levels were measured before and after exposure in the test room and in the unexposed control room. (Papers III–IV). This was done in 96 well plates either by cytopathic effect (CPE) by tissue culture infectious dose 50% (TCID50) determination of both MNV and FCV, and in 6 well plates by plaque assay of only MNV. Intracellular minus-strand RNA was used in addition to the CPE based assay the fourth study to determine the end point of MNV infectivity in an observer independent way (Paper IV). This method which is based on cell lysates after virus replication has occurred is described below. The viral infectivity titres were calculated according to Reed-Muench[169].

3.2.8 PCR methods in Paper IV

The human viruses, (HuNV RNA) were detected by hydrolysis probe Taqman quantitative PCRs (qPCR) performed at our clinical routine diagnostic laboratory essentially as described by Kageyama *et al.*[62] and Logan *et al.*[154] Viral RNA was extracted from 200µL of 10% feces solution using a MagNA Pure 96 Instrument (Roche) and a viral NA small volume kit and eluted in 100 µL of H_2O.

Reverse transcription and hydrolysis probe qPCRs for HuNV I and II, respectively, were conducted separately on 5 µL of purified RNA using a 7500 Fast Real-Time PCR System (Applied Biosystems) with a Path ID Multiplex One-Step RT-PCR Kit (Ambion, Life Technologies). For HuNV I, a VIC probe was used and for HuNV II, a Cy6-probe was used.

Reverse transcription was carried out at 48 °C for 10 min. Reverse transcriptase inactivation/initial denaturation was performed at 95 °C for 10 min. Amplification was repeated 45 times at 95 °C for 15 s and 55 °C for 45 s.

For direct detection of the Murine MNV, also a hydrolysis probe Taqman qPCR method was used on dried and then reconstituted samples exposed to H_2O_2 and in untreated controls. Viral RNA was extracted from 140 µL of reconstituted virus suspension (see below) by use of a QIAamp viral RNA mini kit (Qiagen, Valencia, CA, USA). RNA was eluted in 50 µL of H_2O, and purified RNA samples were stored at –80 °C until used for PCR.

Prior to quantitative RT-PCR, extracted RNA was treated with DNase-I (Thermo Fisher, USA) Reverse transcription followed by quantitative PCR was performed using a SuperScript III One-Step RT-PCR System with Platinum Taq DNA Polymerase (Thermo Fisher). Each reaction (final volume 20 µL) contained 5 µL of DNase-I-treated RNA, 1µL of 4-mM VIC-MNV probe, and 1 µL of 50-ng/µL forward and reverse primer on a Step One Plus (Applied Biosystems) instrument, as described by Lee *et al.*[155] and in the protocol supplied with the one-step kit. Reverse transcription was performed for 30 min, directly followed by denaturation at 95 °C for 10 min and then 45 cycles of denaturation for 10 s at 95 °C, annealing for 20 s at 50 °C, and elongation for 30 s at 72 °C.

As an alternative assay for MNV quantification in the dried HPV/mock treated medium samples, we also used the plus strand variant of a strand specific SYBR green PCR assay as described in detail following the report by Vashist et al.[156] (see below).

Finally, to have an observer-independent evaluation of MNV viability in cell culture, we applied detection of intracellular minus-strand replicating MNV RNA in RAW cells which had been challenged with aliquots of the same material as used for TCID50 determination and direct RNA quantification. In Paper IV we used the

method described by Vashist et al.[156] to detect intracellular minus-strand RNA after cell growth. The background is that noroviruses like many other viruses replicate via a minus-strand RNA intermediate. Such an intermediate is present only in infected cells and can be employed as a marker of active replication of virus in a cell system.

Cells exposed to serial dilutions of our test inocula were grown in 24 well plates. This was followed by removal of culture medium, washing once with PBS, and adding 350 µL of Buffer RLT from the RNeasy mini kit (Qiagen) to achieve lysis. Thereafter, RNA was extracted according to the protocol of the RNeasy mini kit. Purified RNA was eluted in 50 µL of H_2O and stored at –80 °C until used for PCR.

Minus-strand-specific qPCR with one tagged primer was done as described by Vashist *et al.*[156]. Prior to cDNA synthesis, RNA samples were treated with DNase, after which reverse transcription was conducted using the minus strand targeting tagged primer TnegGneg. The 20 nucleotides in the 3´ terminus of this primer are target-specific for the MNV negative strand corresponding to positions 1678–1697 of MNV, whereas the 21 5´-teminal nucleotides are non-viral and used as a tag. We used this composite primer at a low final concentration (0.1 µM) for initial cDNA synthesis using Superscript III at 55 °C. Thereafter, we performed qPCR with SYBR Select Master Mix (Applied Biosystems) using a primer identical to the non-viral upstream sequence and a downstream MNV-specific sequence (Table 2), both at a concentration of 1.0 µM.

For both the minus strand-specific qPCR and the plus strand variant mentioned above the procedures involved initial incubation at 50 °C for 2 min and 95 °C for 2 min, and then 45 cycles of denaturation for 15 s at 95 °C, annealing for 15 s at 58 °C, and elongation for 30 s at 72 °C. Specificity and sensitivity controls consisting of single minus- and plus-strand MNV RNA transcripts were generated as described by Vashist *et al.*[156]The limit of quantification was stable at 250 copies per reaction.

Considering appropriate time points for optimal minus-strand detection, Vashist *et al*.[156] used first-phase growth conditions with high infectious doses and murine BV-2 microglia cells and found maximum levels of minus-strand RNA about 12 h post infection (p.i.). During test development, we made similar observations in RAW cells at high infectious doses. We used low doses obtained by serial dilution of samples, which enabled us to identify reactive wells for up to 72 h p.i. and hence we harvested cultures after both overnight (17-h) and 72-h incubation.

Table 2. Primers and probes used for human norovirus (HuNV) and murine norovirus (MNV) RNA detection in the present study

Virus and assay	Function	Primers and probes
HuNV GI Taqman PCR	Reverse forward probes	5´-TCCTTAGACGCCATCATCATTYAC 5´-ACGCCACTCCGCACAAA VIC-5´-AGATYGCGATCYCCTGTCCA-MGB/NFQ and VIC-5´-AGATCGCGGTCTCCTGTCCA-MGB/NFQ
HuNV GII Taqman PCR	Reverse forward probe	5´-TCGACGCCATCTTCATTC 5´-CARGARBCNATGTTYAGRTGGATGAG CY5-5´-TGGGAGGGCGATCGCAATCT-BHQ3
MNV Taqman qPCR	Reverse forward probe	5´-ACGCCACTCCGCACAAA 5´-CGCGCCAGAGACCACAAA VIC-5´-AGCCCGGGTGATGAG
MNV minus strand specific SYBR green PCR	RT upstream (TnegGneg)	5´-GGCCGTCATGGTGGCGAATAATGGACAACGTGGTGAAGGAT
	Nonviral	5´-GGCCGTCATGGTGGCGAATAA
	MNV specific downstream	5´-GCTTTTGGCCTCACCTCTG
MNV plus strand specific SYBR green PCR	RT downstream (TposGpos)	5´-CGGGAAGGCGACTGGAGTGCCCAAACATCTTTCCCTTGTTC
	Nonviral	5´- CGGGAAGGCGACTGGAGTGCC
	MNV specific upstream	5´- TGGACAACGTGGTGAAGGAT

VIC and CY5 are fluorophores: MGB/NFQ Minor Grove Binding/Non Fluorescent Quencher; BHQ Black Hole Quencher,

3.2.9 Design of experiments

Study II, III and IV were performed in three repeated test rounds.

The head-to head study (Paper II) assessed which system (HPV or aHP) that was most efficient in killing BIs. The BIs were placed centrally and in both high and low positions, using 20 positions in the first test and 14 in the subsequent two tests. The tests included challenging positions, such as on top of a linen cupboard and behind the decontamination apparatus.

In the investigation presented in Paper III, dried FCV and MNV were tested in separate experiments and only HPV was used. In each test run, three 35-mm-diameter wells were used at each position with adjacent BIs. Virus plate/BI combinations were placed at six positions, some of which were regarded as

challenging (see above). In each exposure experiment, the non-HPV-treated patient room was used to determine virus recovery without HPV exposure and as the basis for calculating the reduction of infectivity by HPV. Two control plate/BI sets were used. The lowest measurable titer was defined as the detection limit multiplied by the dilution factor.

In Paper IV, preparations of HuNV GI, HuNV GII, and MNV (higher- and lower-titer preparations designated T and ST, respectively) plus a preparation with an equal volume of MNV ST and HuNV GI, and the spore BIs (all in duplicate or triplicate) were treated with HPV in a test chamber. Controls were mock treated under the same physical conditions. The analyses of HPV-treated and mock-treated samples included direct detection of HuNV and MNV by qPCRs (hydrolysis probe (both) and SYBR green (MNV)). MNV viability reduction was subsequently assessed after HPV treatment on aliquots of the same dried well material both by CPE/TCID50 determination, and also by detection of replicative minus-strand RNA of cell lysates, because such an RNA population verifies active virus growth.

4 Results

4.1 Macro perspective

The new Infectious Diseases Building in Malmö has now (i.e., in 2017) been in use for 7 years, and a preliminary evaluation can now be conducted to elucidate the described planning process and some functions. Active involvement of users and infection control specialists was important in the design and construction process, and the architectonic term for this is co-design or shared decision-making[157]. It is apparent that the full-scale patient room mock-up was cost effective, because expensive mistakes during the building process were avoided[158]. The mock-up room also served as a place where staff could assess and begin adapting to their future work environment. Some examples of changes made due to suggestions offered by staff who had visited the mock-up are as follows: enlargement of the outer airlock because it was first considered to be too small; partitioning the window in the patient room to avoid an "aquarium feeling"; taking into account the importance of avoiding air leakage between the rooms during the construction process (e.g., by not drilling holes in the walls); creating a sufficiently spacious area for handling medications and equipment in the inner airlock; improving the possibility for nurses to keep watch over patients by including a window between the patient room and the corridor. All these aspects have proven valuable in actual practice.

The manifest results of the assessments performed in relation to the three planning principles (i.e., far away and yet nearby, flexibility, and defined links) are presented below.

Applying the principle of *far away and yet nearby* has led to patient rooms with separate ventilation and separate entrances from a balcony running along the entire exterior of the building to create three floors of isolation units in the main hospital area. The floors are reached through ventilated decontaminable elevators. This system has functioned well, and, since the opening of the facility, the only documented spread of an infection involving common pathogens at the Infectious Diseases Department was the spread of *enterococci* via a mobile bladder scanner. We have also dealt with suspected cases of Ebola and multi-resistant tuberculosis, during which the staff felt safe and the isolation system ran smoothly without complaints or deviations.

An infectious diseases ward with a general structure adheres to the principle of *flexibility* in use.

The flexibility principle prompted construction of large single-patient rooms that could be used as double rooms if necessary. This feature has proven useful during the influenza season and also to solve the general shortage of patient rooms at our hospital. More specifically, the infections diseases wards have on occasion housed 27 patients rather than the intended 17 and, due to this flexibility, has been used to temporarily house patients that were moved from other wards that were being renovated as well as infected children from the Department of Pediatrics. The rooms have functioned well for both high-grade isolation and every day care.

Considering the principle of *defined links*, the decision to include transport and entry to patient rooms from the outside balcony has worked well during winter and adverse weather. The risk of spread of infections has been minimized by directing the flow of patients from the outside to isolation rooms in the emergency unit, and from there via the balcony system to rooms in the infectious diseases ward. Patient transports to operating rooms and the ICU have also reduced the risk of spreading infections. No incidents of dispersal of contagious diseases have been reported, except when the single-patient rooms have been used as double rooms.

Figur 10.
Area with isolation rooms with entrance from outside both in the emergency department and in the outpatient clinic for infectious diseases. Patients can be transported directly from the examination rooms to the lifts, and then further to the patientrooms via the balcony system. Photographer Roger Lundholm.

Comments made by the staff regarding the new facility at follow up after 6 months and 12 months concerned issues such the following[159]:

On a negative note, the long walking distance and lack of overview.

From a positive perspective, patient rooms that are suitable and large, modern, fresh and aestethic and in good taste, secure for care of infected patients, and have good lighting, and also that centralization of all functions of the department in one building is beneficial.

The awareness of the importance of already initiating isolation of patients who are being treated at the emergency unit has improved since more isolation rooms were created at that department and the staff began to identify themselves as the first link in an isolation chain.

4.2 Micro perspectives

4.2.1 Head-to-head study: HPV vs. aHP (Paper II)

When using HPV, the peak hydrogen peroxide concentration was 338 ppm; the total cycle time including aeration was 3 h; and all BIs were inactivated in each of the three tests. With aHP, the peak hydrogen peroxide concentration was approximately 100 ppm in the first test, 130 ppm in the second, and 150 ppm in the third. BI inactivation was only 10% in the first test compared with 79% in the second and third tests. The average total cycle time was approximately 3.5 h. In this testing, HPV was superior to aHP in inactivating 10^6 *G. stearothermophilus spores* BIs from a full-scale patient room and also had a shorter cycle time.

4.2.2 Inactivation of BIs (Papers III and IV)

All BIs indicated in Paper IV and most of those in Paper III were inactivated by HPV, which implies satisfactory and even distribution. The only exception was one case in the latter study, when the fan was directed in the wrong direction, although in that case the adjacent virus tests were inactivated.

4.2.3 HPV inactivation of FCV and MNV (Paper III)

In this study, a peak HPV concentration was reached between 474 and 505 ppm. The total cycle time was approximately 3 h. Considering inactivation of viruses, no

viable FCV or MNV was recovered from any of the triplicate wells at any position in the HPV-treated room in any of the three test runs. However, as expected, in all three runs, there was growth of both FCV and MNV from all triplicate wells placed at each position in the mock-treated control room. For FCV, TCID50 assay indicated at least a 3.65-log reduction in infectivity, calculated by subtracting the lowest measurable titer (here ≤ 1.0) from the mean titer of untreated controls (i.e., 4.65). For MNV, a similar reduction of at least 3.67 log was indicated by TCID50, and the plaque test showed a 2.85-log reduction.

4.2.4 Paper IV

A maximum hydrogen peroxide level of 860 ppm was reached at a gassing time of 33 min and the dwell time was 50 min.

We compared the results of qPCR performed to determine levels of RNA from different types of norovirus. Using a Taqman qPCR specific for HuNV I and II indicated that, compared to controls, there was a decline of about 1 Ct (i.e., only a twofold reduction) step after HPV treatment as compared to controls, whereas the reduction was about 4 Ct steps for the mixed sample (HuNV+MNV). In the similar MNV hydrolysis probe Taqman qPCR, there was a change of about 6 Ct steps after HPV treatment. However, when MNV was instead assessed by a plus-strand-specific MNV qPCR using SYBR green as an alternative test for the dominant RNA species (plus strand), only minor differences were observed in Ct values between HPVtreated and untreated samples. (Table 3.)

When assessing MNV viability reduction, we found that TCID50 assay indicated no CPE after HPV treatment when samples were tested in duplicate at 10^{-1} dilution. Since neither of two samples was positive, a highest titer of $\leq 10^{-0.5}$ can be assumed. The highest-titer starting preparation (T) under mock conditions yielded titers of $10^{-5.5}$. The lower-titer preparation (ST) consistently reached a titer of $10^{-4.5}$. With a lowest detection limit of $10^{-0.5}$ due to the starting dilution, the reduction in infectivity was 5 to 4 $\log_{10}$ units. (Table4.)

Reduction of MNV viability was also determined as loss of intracellular replicating minus-strand RNA. No minus-strand RNA was detected in lysates of cells exposed to suspensions prepared from HPV-treated wells diluted 10^{-1}, and the level of reduction was 3.5 to 4.5 $\log_{10}$. (Table.5)

Table 3. Influence by Hydrogen Peroxide Vapor (HPV) on viral RNA in dried human and murine norovirus samples, analysed on reconstituted material by different direct qPCR methods. HuNV GI and GII were investigated in separate. An HuNV GI + MNV mix was also tested for HuNV and MNV RNA. MNV RNA alone was investigated with two independent methods

		Untreated	Treated	Changes	
PCR	Virus	Mean Ct	Mean Ct	log_2 (= Ct)	log_{10}
HuNV PCR	HuNV GI	28	29.6	1.6*	0.48
	HuNV GII	33.8	33.5	-0.3*	-
	HuNV GI + MNV ST#	28.8	33.1	4.3	1.3
MNV PCR	MNV T#	18.6	23.0	4.4	1.3
	MNV ST#	23.2	29.3	6.1	1.8
	HuNV GI + MNV ST#	23.2	27.7	4.5	1.4
MNV Plus strand PCR	MNV T#	16.3	17.6	1.3	0.39
	MNV ST#	20.9	21.6	0.7	0.21
	HuNV GI + MNV ST#	31.8	32.2	0.4	0.12

MNV T- original high titre batch; MNV ST – batch with a tenfold lower titre after repeat passage

Samples containing culture medium

* Mean change 1.3 Ct steps which corresponds to 0.4log_{10}

Table 4. HPV influence on viral (MNV) viability based on cytopathic effect (CPE).
Endpoint sample dilutions giving 50% CPE are shown.

	Untreated controls		**HPV treated**		**log_{10} reduction**
Virus	**Infectivity (raw data)**	**Mean Infectivity**	**Infectivity (raw data)**	**Mean Infectivity**	
HuNV GI	n.d.	n.d.	n.d.	n.d.	
HuNV GII	n.d.	n.d.	n.d.	n.d.	
HuNV GI + MNV ST	n.d.	n.d.	n.d.	n.d.	
MNV T	$10^{-4.5}$ $10^{-6.5}$	$10^{-5.5}$	$<10^{-0.5}$	$<10^{-0.5}$	5.0
MNV ST	10^{-4} $10^{-4.5}$	$10^{-4.25}$	$<10^{-0.5}$	$<10^{-0.5}$	3.75
HuNV GI + MNV ST	n.d.	n.d.	n.d.	n.d.	

Table 5. HPV influence on viral (MNV) viability based on end points of intracellular minus strand RNA production. After 17 and 72 h, respectively, cells were washed, lysed and tested for intracellular minus strand. RNA. Ct values above end points are shown in bold.

		Untreated				HPV treated			
Virus	**Dilution**	**Mean Ct values 17 h**	**Mean Ct values 72 h**	**Mean Infectivity 17h**	**Mean Infectivity 72h**	**Mean Ct values 17h**	**Mean Ct values 72h**	**Mean Infectivity**	**log_{10} Reduction**
HuNV GI		n.d.				n.d.	n.d		
HuNV GII		n.d.				n.d.	n.d		
MNV T	$1:10^{-1}$ $1:10^{-2}$ $1:10^{-3}$ $1:10^{-4}$ $1:10^{-5}$ $1:10^{-6}$	**21.6** **24.5** **288** **360** 42.5 42.4	**23.7** **210** **16.8** **211** **21.1** 42.5	$10^{-4.}$	$>10^{-5}$	41,9 42.9	UD 42.8	$< 10^{-0.5}$	>4.5
MNV ST	$1:10^{-1}$ $1:10^{-2}$ $1:10^{-3}$ $1:10^{-4}$ $1:10^{-5}$ $1:10^{-6}$	**24.4** **25.6** **37.2 29.6** UD* **38.7** UD 39.0 UD 41.2	**23.2** **21.5** **21.8** **19.5** 42.8 40.3	$10^{-3.5}$	$10^{-4.5}$	41.3 40.9	41.3 42.4	$< 10^{-0.5}$	>3.5-4
HuNV GI +MNV ST	$1:10^{-1}$ $1:10^{-2}$ $1:10^{-3}$ $1:10^{-4}$ $1:10^{-5}$ $1:10^{-6}$	**24.0** **27.9** **30.5** 43.5 43.2 43.1	**26.8** **21.5** **22.2** UD 44.8 UD	$10^{-3.5}$	$>10^{-3}$	43.7 44.7	43.5 44.5	$< 10^{-0.5}$	>3.0

* Undefined, interpreted as negative.

Displayed Ct values are the mean of two parallel PCRs from each well. Two values are shown if values are discrepant from two parallel wells.

6 Discussion

6. 1 The planning and building process

Inasmuch as we had thoroughly documented the process of planning of the new infectious diseases facility in Malmö, it was possible to write a descriptive report outlining the entire undertaking, when we subsequently realized that there was a demand for the data we had gathered and our experiences in this context. We realized that it is methodologically very difficult to perform a before-and-after study of this kind of project, because there are so many parameters that differ between a new facility and its earlier counterpart. This is a problem that is well recognized in scientific evaluation of architecture. In addition after our unit moved into the new facility in 2010, many organizational changes were made, such as fusion of the two university hospitals in Malmö and Lund and changes in both staffing and patient case mix. Due to a shortage of beds in the hospital in Malmö, the desired single-room concept has been abandoned, and the number of patients on each floor is higher than was originally planned. This is an important lesson to be learned, noting that the probability of changes in the organization of the healthcare system is now so pronounced that there is a substantial risk of unplanned use of a building tailored for a particular purpose. For example, if we had known that so many of the rooms would have to be used as double rooms, we probably would have suggested a less flexible solution comprising more small single rooms. It might be beneficial to construct a mock-up care unit, particularly when planning a specialized facility such as an infectious diseases ward, both to help builders avoid repeating previous mistakes and to give the healthcare staff the possibility to influence the planning of the construction of the building.

An aspect that is now under debate is whether to build only single rooms in intensive care units since they are the facilities that would benefit most from having single-patient rooms from a infection control point of wiew. On the other hand such units are the most costly and most staff-intensive to run, and there is also a lack of staff with the appropriate training. In part, it can no doubt be concluded that a larger proportion of single rooms is needed in intensive care facilities.

6.2 Hydrogen peroxide

According to earlier investigations[136, 139], hydrogen peroxide systems are the most efficient NTD methods, and they are environmentally friendly because hydrogen peroxide is degraded to oxygen and water. A potential problem that should be mentioned is that some aHP systems include silver to stabilize droplets, which can enhance antibiotic resistance, even if only small amounts of silver are used[160].

A strength of two of our studies (Papers II and III) is that we used full-scale patient rooms to make the testing more realistic, and we placed BIs and viruses in positions that were difficult to reach and hence rendered the tests more challenging. The rationale for using 10^6 *G. stearothermophilus* BIs is that this approach is standardized, simple to perform, and widely employed for measuring decontamination.

Spores are considered to be the microorganisms that are "the most difficult to kill" compared to bacteria and viruses. An important question is whether this organism at this amount is too difficult to inactivate, but we consider it wise to have margins when decontaminating a room[161]. The superior results obtained with the HPV described in Paper II might be explained by the peak hydrogen peroxide concentration being maintained for a longer time, or perhaps it was the smaller droplet size that facilitated spreading of the hydrogen peroxide to parts of the room that were difficult to reach. Our results showing superiority of HPV have subsequently been confirmed by other researchers using BIs and also test discs prepared with MRSA, *C. difficile*, and *Acinetobacter baumannii*[162]. Furthermore, a recent study recorded equivalent results for two HPV systems, one using 30% HPV and with the other 4.9% HPV[163].

To investigate viruses, we chose to use FCV and MNV as surrogate markers for HuNV, which was only recently cultivated for the first time[61]. FCV is a feline respiratory virus that has been used in several inactivation studies, although another virus that is more similar to HuNV is MNV, which infects and is shed via the gastrointestinal tract of mouse. We decided to use both FCV and MNV in order to cover a broader spectrum. Both these viruses are harmless to humans and thus are easy to handle in test situations and in the laboratory. Our inactivation findings confirm the results that Tuladhar et al. obtained using HPV in an isolator to inactivate MNV[87]. Tuladhar and colleagues tested several viruses dried on stainless steel, framing panel, and gauze carriers, whereas we used viruses dried on plastic labware because we considered such material to be more similar to surfaces in a hospital room.

The use of qPCR on material collected on surfaces or in fluids to measure virus inactivation has a number of pitfalls. Accordingly, after conducting our FCV and MNV inactivation studies using CPE as a marker, we were interested in determining whether virus inactivation would be reflected in the qPCR levels for two reasons: (I) to consider the value of qPCR as a strategy for measuring the success of HPV inactivation of viruses including human noroviruses; (II) because several investigations have used qPCR to demonstrate the spread of RNA from noroviruses present in proximity to patients in hospitals, thus giving rise to the question of whether the qPCR findings actually represent or may not represent viable virus.

We assumed that the norovirus genogroups HuNV GI and GII and MNV V are structurally so similar that the HPV inactivation of MNV measured by two methods (TCID50 and intracellular minus-strand RNA) parallels the inactivation of HuNV. In our assessment, there was a limited decline in RNA levels in the faeces, mixed or medium based samples recovered from the dry plates for all the tested viruses, and qPCR findings on HPV-exposed surfaces did not reflect the level of inactivation. Moreover, it seemed that the presence of culture medium surprisingly played a role in combination with H_2O_2 when using qPCR protocols that included hydrolysis probes. Hence the impact of HPV increased more than expected (1 Ct step) when the HuNV GI fecal samples were diluted 1:2 in culture medium. Concomitantly, HPV caused a 5–6-Ct step increase on MNV (in medium) according to a qPCR assay based on a hydrolysis probe, Interestingly no such effect was demonstrated when a SYBR green plus-strand qPCR assay was conducted of the same sample. For a plus-strand RNA virus such as MNV, a qPCR that is specific for plus-strand RNA should essentially detect the same dominant viral RNA species as a diagnostic qPCR, because the virus particles will only contain plus-strand RNA. We used MNV particles released into medium as the starting material in our HPV exposure experiments.

The above-mentioned data demonstrate that HPV exposure leads to some minor loss of viral RNA, in stark contrast to the strong effect on MNV viability.

PCR has been used to investigate the presence of HuNV in the environment, and it is not unlikely that a discrepancy exists between detectable viral RNA levels and viable virus that is similar to the disparity we noted after HPV treatment. It is interesting that HPV does not have an even greater impact on RNA levels, considering that one of its modes of action is to function as an antioxidant against viruses by producing hydroxyl free radicals that attack proteins, lipids, and nucleic acids[144]. Zonta et al.[164] observed that the correlation between inactivation measured by cell culture methods and that determined by PCR differs depending on the types of virus investigated and the inactivation techniques that are used.

Our results regarding MNV are in line with data reported by Tuladhar et al.[87] showing virucidal efficacy of HPV against several viruses, including MNV, as

measured by TCID50 based on CPE. Among the viruses tested by those authors, there was only a small or even undetectable reduction in PCR signals after HPV treatment, and the most limited reduction was noted for HuNV (i.e., the decrease was even smaller than for MNV), which agrees with our observations.

In contrast to our studies, Zonta et al.[165] used only aHP, not HPV, but reports have indicated that HPV is superior to aHP for combating bacteria and spores[162, 166]. The findings presented by Zonta and coworkers concur with our observations in that they demonstrate virucidal efficacy against MNV and FCV but only a small reduction in PCR levels.

Neither of the two research groups mentioned above (Tuladhar et al.[87] and Zonta et al.[164, 165]) used detection of replicating viral RNA to monitor residual viral growth. The reason for us to chose minus-strand RNA detection was to overcome the difficulty in using CPE to determine the endpoint of infectivity. In our hands, CPE-based assessments, including those using the plaque assay approach, were highly dependent on rapid passage of the RAW cells (three times weekly), optimal cell numbers at seeding, and an appropriate density of about 50% when infected. If these criteria are not met, the initial CPE can disappear due to overgrowth. Monitoring virus growth by use of PCR specific for replicating RNA is a robust method that is not influenced by subjective interpretation based on examination in a light microscope. We found good agreement between CPE and minus-strand detection.

Another important aspect that can be discussed is whether it is better to lease or to buy the hydrogen peroxide systems. Based on observations made during our field trips, it seems that leasing is the best option for short-term decontamination during an outbreak, whereas purchasing a system is the best alternative for long-term use. The field trips also gave the impression that it is advisable for the systems to be run by specially trained cleaning staff.

Also of interest, it can be beneficial if the construction of a hospital building can enhance the use of hydrogen peroxide by planning rooms that are both easy to seal and have ventilation that is simple to turn off.

...it can be beneficial if the construction of a hospital building can enhance the use of hydrogen peroxide by planning rooms that are both easy to seal and have ventilation that is simple to turn off.

6.3 Comparing performance of different types of studies

It has been very interesting both to carry out the present studies and to write a paper that is markedly different from the type usually seen in the field of medicine. It has also been highly stimulating to note how much easier it is to conduct a conventional investigation with a limited research question than to describe and study a more complex process such as the design and construction of a building, even though it is definitely very important to gain as much knowledge as possible when evaluating that type of process.

7 Conclusions

We are approaching a post-antibiotic era, and infection control is becoming increasingly important[3, 5]. There is no single measure that can solve the problem of slowing the development of resistance in microorganisms. Consequently, work must be done from all perspectives—from a macro to a micro level—to find ways of minimizing the spread of infections and resistant bacteria. There are plans to build many new hospitals worldwide in the near future[96], and therefore it is important not to miss the opportunity to achieve the design and construction of the facilities in a manner that will diminish the risk of spread of infections and to consider this to be a vital part of the process. Infection control measures should be given top priority in all hospital design, and it is essential that the infection control team is involved early in the planning of a new facility.

Indeed, numerous aspects must be taken into consideration in this context. For example, the flow or movement of patients with contagious diseases should be organized in ways that reduce the risk of transmission. Emergency departments should have single-patient isolation rooms with individual entrances from the outside. The transport of patients from an emergency department to an infectious diseases department can be organized outdoors, and entrances to the patient rooms can be from an exterior balcony in multi-story buildings. Furthermore, it is possible to design patient rooms with substantial flexibility that renders them suitable both for high-level isolation to prevent airborne diseases and for everyday care. Standardization and use of a full-scale mock-up are effective measures to minimize unnecessary and costly changes during the process of designing and constructing a hospital building, and standardization also enhances patient safety[167].

Anterooms are necessary to ensure the stability of advanced ventilation systems[168]. In addition, including a large proportion of single rooms can help avoid the spread of infections[39, 103]. Due to the use of modern ventilation techniques and proper planning of patient flows and entrances from the outside, it is now possible to place isolation units within the central areas of a hospital.

When designing units for infectious diseases, a high degree of flexibility is a key factor in order to be prepared for seasonal variations, epidemic outbreaks, and a changing panorama of infectious diseases and carriage of resistant bacteria. Antibiotic stewardship and hand washing/disinfection and conventional cleaning are all very important, but when those efforts are not enough (i.e., when facing

pathogens that are particularly dangerous, difficult to kill, and/or have a low infectious dose), it is necessary to consider using NTD for terminal disinfection. To date, it seems that the most useful NTD systems are based on hydrogen peroxide, and HPV appears to be the most efficient option. It can be a good idea to plan facilities in a manner that will enhance the use of hydrogen peroxide (e.g., as mentioned above, include rooms that are easy to seal and have ventilation that is easy to turn off).

Noroviruses and sapoviruses are common pathogens that have a low infectious dose, can survive for long periods on surfaces, and can be airborne[29]. The successful eradication of the two surrogate viruses used in the present studies suggests that HPV can be a useful tool for decontamination of surfaces contaminated with norovirus and sapovirus in patient rooms and thereby prevent nosocomial spread to subsequent patients. We also noted that qPCR levels recorded after HPV treatment do not reflect inactivation of MNV, and that finding can probably be extended to HuNV. Furthermore, we observed that detection of intrcellular production of minus-strand MNV RNA was a useful marker for evaluating reduction of MNV viability in cell cultures, and thus this methodology may prove to be useful if HuNV cell culture becomes more readily available.

8 Future research

Together with investigators at Ingvar Kamprad Design Center at the Faculty of Engineering (LTH) of Lund University, we have started research on the spread of airborne infections, using naturally occurring norovirus outbreaks as a model. We are addressing the question of whether there are any differences between wards with clusters of norovirus infections and other wards in terms of ventilation, airflow, humidity, and the presence of virus in the air and on surfaces measured by PCR. We are also developing a model based on aerosolized murine norovirus to assess the spread and survival of viruses in the environment.

We also intend to conduct additional head-to-head studies using new hydrogen peroxide systems and a wider range of pathogens. Planning is underway to construct numerous new buildings in the Skåne region, and we are working on identifying parameters of the construction process that can be evaluated in our research.

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Sofie och Martin- jag har inte påverkat ert yrkesval men entusiasm kanske är lika smittsamt som vissa infektioner?

Linn tack för att du fortfarande bor hemma och förutom allt annat att du med din tonåriga argumentationsförmåga håller igång mitt intellekt.

Charlotte min livskamrat för kärlek omsorg och visat tålamod under avhandlingsperioden

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Paper I

Design for the Post-Antibiotic Era: Experiences from a New Building for Infectious Diseases in Malmö, Sweden

Torsten Holmdahl, MD, and Peter Lanbeck, MD, PhD

ABSTRACT

OBJECTIVE: To describe the experience of planning and designing a new facility for infectious diseases in Sweden and to discuss underlying theories relating to infection prevention and evidence-based design.

BACKGROUND: Departments of Infectious Diseases are common in healthcare facilities in Sweden. In 2005, a decision was made to build a new facility. The program required spacious single rooms, with a high ventilation standard, and anterooms.

METHODS: In this article we present an analysis of the future of infectious diseases. Underlying theories are discussed. We also describe how a program was outlined using literature studies, including evidence-based healthcare design, focus groups of staff, and study visits.

RESULTS: Active involvement of users and infection control specialists was important in the building process. A full-scale patient room mock-up was built with ventilation, electrical, and other systems. The mock-up was cost effective because it avoided costly mistakes during the building process. The mock-up also was a place where staff could assess and begin adapting to their future work environment. Separate ventilation and separate entrances to patient rooms from the building exterior allowed placement of isolation units in the main hospital area.

CONCLUSIONS: Antimicrobial resistance, emerging diseases, healthcare associated infections, and outbreaks highlight the need for infection control measures in all hospital design. Infection control should be integrated in all hospital planning and be part of contracts. In this study we describe a specialized unit where a high degree of standardization and flexibility has made it possible to have a unique standard of preparedness for the post-antibiotic era.

KEYWORDS: Design process, evidence-based design, infection control, planning, safety

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In 2010, a new Department of Infectious Diseases was opened in a university hospital (see Figure 1). In this article we will share the ideas and experiences of creating such a facility for an era in which antibiotic resistance has increased to a level where common bacterial diseases can no longer be treated with antibiotics. In such a "post-antibiotic era," more patients have to be isolated to avoid spread of resistant bacterial strains. The new facility was also designed to address emerging infectious diseases and for outbreak capacity, such as in the case of pandemic influenza or SARS-like disease. Some features of this experience could be of interest for the international community.

Background

Sweden has a long tradition of building separate facilities for infectious diseases (ID) and isolation care. Unlike in many countries, ID is a speciality on its own in Sweden, not a sub-speciality of internal medicine. The proportion of beds in ID facilities, in relation to the total number of hospital beds, is higher in Sweden than in other countries. Not only are patients who need to be isolated cared for but also patients with, for example, pneumonia, urinary tract infections, etc.

Compared to North America and the United Kingdom, the prevalence of multiresistant bacteria has been low in Sweden. There are several reasons for this,

Figure 1. The facility for the Department of Infectious Diseases and for the Emergency Department.

Street level: The entrance to the emergency room is in the middle of the building. The ambulance entrance is on the backside. The outpatient clinic for Infectious Diseases is on the right side.

including that the level of antibiotics used by humans and for livestock has been lower in Sweden for decades than in most other countries. Overuse of antibiotics increases the development of resistance, and inadequate hygiene, overcrowding, and understaffing in hospitals also contribute to increased resistance. In Sweden, crowding and understaffing have been uncommon until recent years and hospital hygiene has remained at a high level.

The proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) of all *Staphylococcus aureus* isolates is lower in Sweden (less than 1%) than in many other European countries (up to more than 40%), and hospital acquisition is uncommon (European Antimicrobial Resistance Surveillance Network, 2013). Carriers and suspected carriers are proactively isolated in single rooms. Recently, the prevalence of other types of bacteria, such as multi-resistant gram-negative bacteria, has increased dramatically, although is currently at a low level compared to many other countries (SWEDRES, 2010). The origin of these types of bacteria is the gut or the environment. Typical bacteria from the gut include *E. coli* and *Klebsiella pneumoniae,* and from the environment *Acinetobacter baumanni* and *Pseudomonas aeroginosa.* In recent years some strains of these bacteria have developed extensive resistance for which there are no, or very limited, therapeutic alternatives.

Many of these agents are spread across borders in the community rather than in hospitals. Through ingestion of contaminated food specimens or water, the gut will be colonized, and resistant bacteria spread by travellers (Tham, Odenholt, Walder, Brolund, Ahl, & Melander, 2010). Therefore, there is reason to expect that the spectrum of resistant infections in comparatively safe countries like the Sweden, Netherlands, and Denmark will continue to rise, and such infections will be brought to hospitals and other healthcare settings.

In the facility discussed in this article, the old ID department was built in 1908, rebuilt in the 1940s, and rebuilt again in the 1960s. In recent years it had 52 beds divided among 18 single rooms and the remaining in double or triple rooms. It serves a regional population of almost 400,000. The facility had become worn out and by modern standards its ventilation and working conditions were substandard. Complaints from patients and their relatives were becoming more common.

In 2005, the hospital management and the regional board decided to build a new facility. The location of the new facility was to be close to the emergency room, which itself would have some sections rebuilt. These two projects were linked and financed together. The decision to integrate a new facility for ID came on rather short notice.

Key Design Goals and Considerations for the New Building

The key design goals and considerations for the new building included the following:

- Safe outdoor circulation (and initial ED admission) of patients.

- A significant number of single rooms.
- High standard for ventilation, including pressurization and filtration.
- A design that protects staff as well as patients.
- Evidence-based design (EBD) used to create a calming, psychologically supportive environment for patients in isolation.
- EBD used to facilitate effective staff work and patient care, and reduce staff stress.

Program Work (Early Planning)

The scenario for ID with emerging diseases, the development toward a post-antibiotic era, and recent outbreaks presented a challenge. Therefore, we decided to actively involve ourselves as ID specialists and also involve the staff of the department. We actively searched for information regarding infectious diseases and infection control with design implications. During this phase we used different approaches to obtain evidence and information relevant to the project, including:

- Literature review.
- Focus groups among staff.
- Visits to other infectious disease facilities.
- External expertise.
- Frequent meetings with the architect and ongoing engagement in the project.
- Consideration of healthcare architecture design precedents from the pre-antibiotic era that might be relevant in the post-antibiotic era.
- Use of mock-ups.

Literature Review

Searches of scientific databases were performed and also a general search of the Internet. Official documents such as guidelines on ventilation standards for tuberculosis care from the Centers for Disease Control and Prevention (CDC) (2005) and building recommendations of the Swedish Association of Infection Control (2010) were important. Some documentation on the isolation standard in the newly built University College of London Hospital (UCLH) was available online, and later appeared as a paper in the *Journal of Hospital Infection* (Wilson & Ridgway, 2006).

We also carefully read the reviews and recommendations from Ulrich, Zimring, Quan, Joseph, & Choudhary (2004). Throughout the project the principles of evidence-based hospital design were an important inspiration for us. We also had the opportunity during this phase to interview professor Roger Ulrich.

Focus Groups Among Staff

Multidisciplinary groups of experienced staff members were created and a creative brainstorming process with active participation of different staff groups was initiated. The initial instruction was to think freely: how would we like a new department to be, irrespective of what we have today? A key goal was to rethink the organization itself, in order to avoid simply moving the traditional organization and care processes into a new, advanced building.

Building issues were on the agenda of all staff meetings, a mailbox for suggestions was placed on the wards, and discussions were promoted among physicians on the theme of the future of ID and the implications for designing the new building.

Site Visits

The most recently built or reconstructed departments of ID were visited to learn from the experiences—good and bad. Infection control solutions such as ventilation, cleaning, placement of sinks and alcohol hand rub dispensers, etc., were evaluated. Some multidisciplinary teams visited departments in nearby regions and countries.

The newly built University College of London Hospital (UCLH) was shown to our project group by Dr. Peter Wilson and colleagues. We would like to underline the importance of international contacts in the process of creating a new ID facility. Their experiences in positioning and involving infection control in the planning and construction of a new building were very important for us. One of their conclusions was that it is essential for users to be active and attend to all meetings, because infection control issues often are overlooked by other participants in the building process (Wilson & Ridgway, 2006).

In recent years, high level bio-containment facilities for high risk isolation have been built in Denmark and Norway, and we also visited these.

External Contacts

Local and national experts in infection control, disease control, and ID were also interviewed, including the chairman of the Swedish Society of Infectious Diseases and the local Public Health Officer.

Future of Infectious Diseases

To better anticipate the coming 25 years, we chose to look back 25 years. In 1980, several diseases and ID problems of today were unknown or had other clinical presentations. Generally a belief prevailed in the medical discourse that ID problems were solved with antibiotics and by improving socio-economic conditions. During the past 25 years there has been a paradigm shift as antimicrobial resistance has fundamentally changed the scene (World Health Organization, 2001). New and emerging diseases like HIV, Hepatitis C, multiresistant tuber-

culosis, *clostridium difficile,* and norovirus are all examples of new and serious problems to consider. Globalization, increased travel, and immigration facilitate the rapid transmission of infectious diseases and resistant bacteria around the world. The outbreak of SARS, with its rapid global migration, highlighted the need for handling patients with isolation precautions in all parts of the hospital (Farquharson & Baguley, 2003). Global warming could mean that diseases become endemic in new areas, which would be relevant, for example, for tick-borne diseases or diseases spread by mosquitoes and other insects. Flooding can also enhance the spread of diarrheal diseases.

Although it is difficult to predict the future, increasing antimicrobial resistance will continue to be a major problem and the fear of a post-antibiotic era is a real concern (WHO, 2001). A high degree of flexibility and preparedness will also be necessary to combat diseases with unknown modes of transmission. The challenge is to create a hospital facility that is prepared for these scenarios as well as for the everyday care of ordinary patients.

Decisions

After analyzing the future of ID, we had more background to help us make necessary decisions about the new building. One important question was the number and type of patient rooms. The need for different types of rooms in a facility for ID is illustrated in Figure 2.

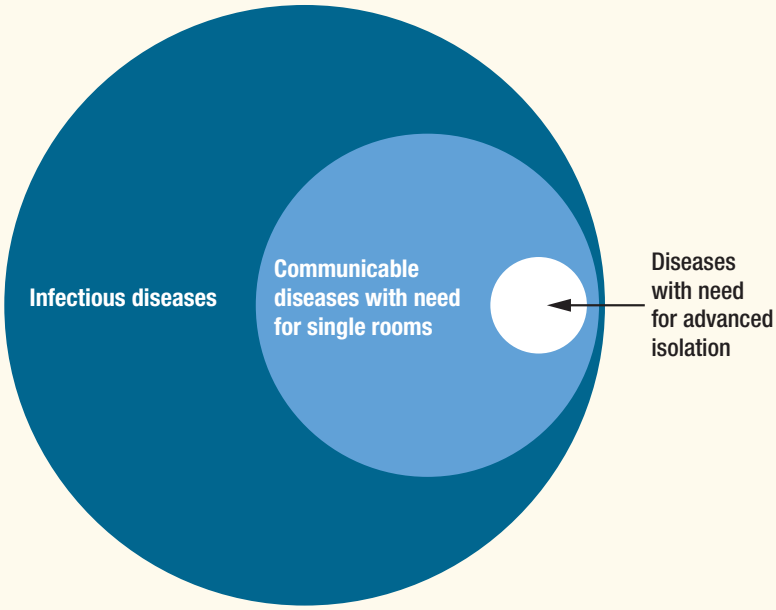
We decided to advocate for a department with 100% single rooms. All information collected pointed to this—the general situation in the hospital, with only about 20% single rooms; the staff's experiences with a shortage of isolation rooms necessitating the transfer of patients between rooms; the expected increase in demand due to spread of antimicrobial resistance, high demands during outbreaks in winter of various illnesses including influenza; and recommendations in the EBD and infection control literature (Ulrich et al., 2004; Wilson & Ridgway, 2006; Stockley, Constantine, Orr, & The Association of Medical Microbiologists New Hospital Developments Project Group, 2006). Although some researchers in infection control various countries are skeptical of the cost-effectiveness of single rooms (Kirkland, 2009), the evidence for single rooms is abundant and strong (Ulrich et al., 2008). Not only do single rooms help prevent transmission of hospital-associated infections (Bonizzoli et al., 2011; Cheng et al., 2010; Cooper et al., 2004; Hamel, Zoutman, & O'Callaghan, 2011; Teltsch, Hanley, Loo, Goldberg, Gursahaney, & Buckeridge, 2011), but evidence also exists for single rooms resulting in increased patient satisfaction, better quality of communication and information, better privacy, less noise, reduction of medical errors, and increased possibility for family visits (Chaudhury, Mahmood, & Valente, 2005; Ulrich et al., 2008). The ethical considerations of this issue, and their effects on decisions taken by hospital management and politicians, have been discussed by Tuckey (2008).

Contact isolation may be associated with negative effects on the psychological well-being of patients and behavior (Abad, Fearday, & Safdar, 2010). There are also negative effects associated with healthcare workers spending less time with

Figure 2. Need for isolation precautions in infectious diseases.

The dark blue circle represents all patients with infectious disease; those patients do not need isolation precautions. The light blue circle represents all patients with contagious diseases that need some kind of isolation precautions. The white circle represents patients with highly contagious airborne diseases with need for a higher level of isolation. The circle sizes vary due to seasonal variations and outbreaks.

Source: Anders Lindberg, MD, Halmstad, Sweden.



isolated patients. Evidence-based design measures can be taken to overcome such adverse effects. For example, rooms should be spacious, allowing for family presence. Light and views are important, visual and vocal communication should be facilitated, and noise reduced.

Another issue to consider is the role of isolation rooms in preventing airborne transmissions (see the white circle in Figure 2). At most times the need for isolation rooms is low, because airborne transmission of microbial agents is less common than droplet transmission or transmission by direct contact. Although some bacteria, such as MRSA and *Acinetobacter,* can become airborne on skin particles after bed making, for example, this has not led to a general view that airborne transmission is a more serious factor to address. Some authors challenge this position (Beggs, Kerr, Noakes, Hathway, & Sleigh, 2008) and recommend a high ventilation standard. We concluded that there is a clear need to be prepared for outbreaks of SARS-like diseases, pandemic flu, or an increased incidence of tuberculosis, and there will be at certain times a great need for isolation rooms. Rooms with a high ventilation standard and negative pressure are complicated to build. No leakage between rooms can occur, there is a need for anterooms, and

Table 1. Simple Description of Infection Control Measures to Prevent Transmission of Microbial Agents

TYPE OF TRANSMISSION	EXAMPLES OF AGENTS	PROTECTIVE GEAR	FACILITY PLANNING
Contact	Bacteria, including resistant strains	Gloves, gown	Sinks and alcohol rub dispensers in many locations, including single rooms
Droplet	Influenza virus	Gloves, gown, and surgical mask	Single rooms
Airborne	Tuberculosis, Varicellae	Gloves, gown, and filtering facepiece (FP) mask	Isolation rooms with controlled ventilation, anterooms, levels of air exchange

ventilation control is complicated (Rydock, Eian, Lindqvist, Welling, Lingaas, 2004; Stockley et al., 2006). These obstacles are easier to overcome in new construction than in renovation. Considering this, standardization of the design of patient rooms could be a significant benefit to the building process as well as to future patient safety and preparedness. Therefore we argued that as many patient rooms as possible should be built with negative pressure.

Seasonal variations in infectious diseases are well documented in the northern hemisphere. For example, influenza and the morbidity of respiratory tract infections vary seasonally, as do outbreaks of gastrointestinal infections. In outbreak situations, a pandemic influenza, for example, the need for beds sharply increases. To increase flexibility in the building to handle outbreaks we argued for spacious single rooms that could be converted to use as small double rooms. Another factor supporting large rooms is the growing perceived need for family support (Ulrich et al., 2008). Large rooms are also more functional for disabled patients.

Design Precedents

Traditionally, pre-antibiotic era infectious disease departments have had entrances to patient rooms directly from the outside, making possible the safe movement of infected patients in outside air. This was the design of the old department in this case. In the old facility there was also an outer anteroom, through which all waste left the wards. Entrance from the outside makes it possible for patients and relatives to enter rooms under isolation measures without entering the interior areas of the ward. The pre-antibiotic era design makes proactive separation of patients with, or with suspected, contagious diseases more efficient, and prevents cross-infection in hospital interiors from unrecognized carriers of disease (Ulrich & Wilson, 2006; Farquharson & Baguley, 2003). This facility's old design also had an inner anteroom through which staff entered a patient's room. Anterooms help secure airflow and ventilation (Stockley et al., 2006) but they also provide a place to promote hand washing and disinfection as normal routine and facilitate donning protective wear and masks.

After thorough discussions about the need for anterooms it was decided that the idea of design standardization supported the need for anterooms. In this way, architectural design precedents from the pre-antibiotic era—including exterior or outside circulation and anterooms—were found highly relevant for the post-antibiotic era. Accordingly, it was stated that as many rooms as possible should be large single-rooms, with en suite bathrooms, and inner and outer anterooms and negative pressure ventilation.

High-Level Isolation

Most countries have high-level isolation facilities dedicated to a few extremely contagious diseases like viral hemorrhagic fevers (e.g., Ebola). A very high standard of isolation is required for these types of cases, but access to a special type of high security laboratory (P4), where highly contagious and dangerous microorganisms can be handled, is also necessary. Training of staff is even more important (Bannister, Puro, Fusco, Heptonstall, & Ippolito, 2009). This type of facility was not requested in this case, but instead a high capability for isolation capacity on a level just below that of high-level isolation units. The idea was to build many rooms capable of isolating contagious patients, but which also could be used for everyday care.

Accordingly, it was stated that as many rooms as possible should be large single-rooms, with en suite bathrooms, with inner and outer anterooms and negative pressure ventilation.

Main Principles

The complex reasoning was distilled into three main principles. These principles facilitated communication in the project, and clarified the message. These principles were used during the entire project and were useful for testing changes and new ideas.

Far Away Yet Nearby

This principle responds to the fact that isolation wards, like the old department in this case, traditionally have been located as freestanding facilities on the outskirts of, or even outside of, the hospital grounds. However, modern standards for ID patients require close proximity to main hospital functions such as ICU, radiology, surgery, and emergency medicine. The new facility was placed close to the emergency room but also the ICU. A long physical distance can be ameliorated in a modern building with technical solutions like separate and advanced ventilation, isolated elevators, separate sewage systems, and exterior entrances to patient rooms (and outdoor air) via circulation balconies.

Flexibility

Following the principle of flexibility, patient rooms can be used both for everyday care and high-risk isolation. Furthermore rooms are of a flexible size, allowing higher occupancy in during seasonal variation situations and in outbreaks.

Defined Links

The principle of defined links means that it should be possible to separate the flow or circulation of patients with contagious diseases from other patient circulation. There should also be defined links for transporting these patients between the ID ward and other facilities such as the emergency department and radiology department.

Building Planning and Construction

Once the architectural firm was selected and project teams were organized, construction began and the building began to take shape.

Architect

The architect competition was won by a firm with experience of designing hospitals in the Scandinavian countries. It cooperated with a local architect firm.

Project Organization

This project was organized by a regional building management organization. One project manager was designated. Planning was lead by another person, and later on a production leader was appointed. The hospital director appointed a project manager for the different user groups involved in the project. In total 11 side projects were started because several hospital functions had to be moved in order to create space for the new building. Interactions between building management and the hospital project organization were defined in a project manual.

The Building

The total construction area was 24,000 square meters, of which 19,000 square meters was new construction and the remaining 5,000 square meters reconstruction.

The building was designed as a round building with balconies on three floors for the ID wards. The emergency department and the ID outpatient clinic were located on the ground floor. Two administrative floors were located above the wards, and the upper floor was dedicated to technical installations, especially ventilation.

The design was untraditional not only in its round shape, but also in its use of colors, glass, and light. It was intended to serve as a distinctive landmark on the hospital grounds and in the city. As is described later, the design included several important creative solutions for the demands of this program.

Planning started in January 2006 and construction began in January 2008. The departments moved in at different points; the ID wards were opened in October 2010, and the ID outpatient clinic in March 2012.

Departmental and Room Planning

Three types of meetings were of great importance during the planning process. The most important were weekly meetings with the architectural firm. A continual dialogue between the project group and the architects, who had much previous experience with hospital buildings, was of utmost importance for achieving the final desired result, as has been described by others (Ballard & Rybkowski, 2007; Stockley et al., 2006; Wilson & Ridgway, 2006). A mutual respect for the different areas of expertise developed.

Meetings between the hospital project group and building management were also of great importance. In these meetings financial decisions were discussed or made, and adherence to governmental and regional rules and regulations was ensured.

Some users also attended planning meetings, during which all consultants on technical issues participated.

As infectious disease physicians we decided to always attend meetings in order to improve our understanding of all parts of the project. It can be argued that a high degree of user influence on or involvement in hospital design could potentially increase costs, since users typically are not aware of the costs involved in different technical solutions, and they may also be prone to introducing many changes. Our view is the opposite: by openness and involvement of users in the early stages, a healthcare building will be more functional and its cost effectiveness over time will be higher (Berry, Parker, Russell, Coile, Hamilton, O'Neill, & Sadler, 2004; Lawson, 2005; McCarthy, 2004). An informed and involved user group can be expected to make sensible decisions. Preventing or limiting user influence in the planning stages can potentially increase hospital operations costs later on, for example, by leading to dysfunctional work processes that create higher running costs for many years. The risk for continuous rebuilding also will be high (Ballard & Rybkowski, 2007).

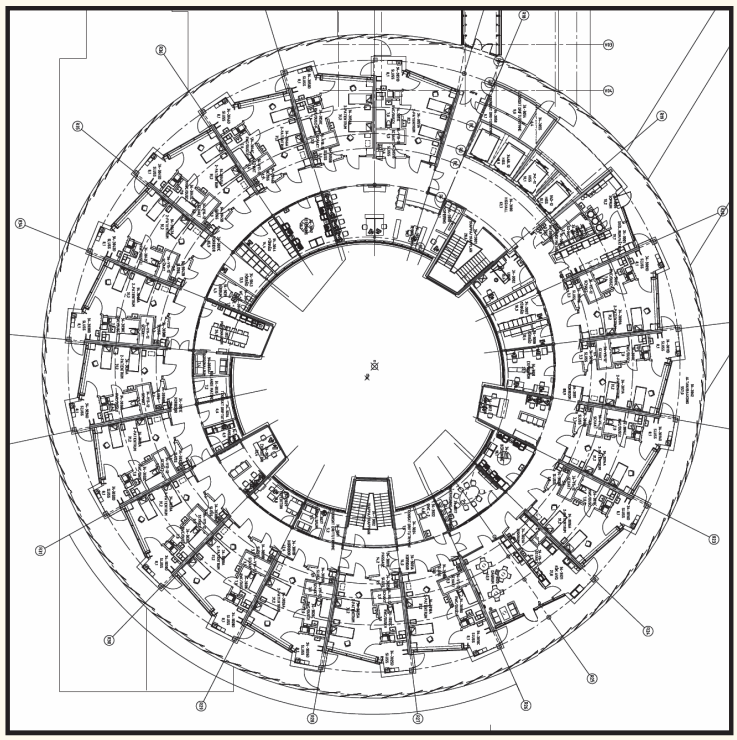
Patient Rooms

The architects presented a solution for the patient room unit that fulfilled the requirements of the function program. Given the limited site area defined for the project, the only possible solution for creating entrances to all 50 patient rooms from the outdoors was a multi-story balcony system. By proposing a round building, a high degree of standardization could be achieved because the patient room units were distributed along the outer perimeter. The patient rooms were identical in size. Nursing offices and stations, staff rooms, supply rooms, etc., were located in the inner perimeter (Figure 3).

The patient room unit consisted of a large patient room, bathroom, and inner and outer anterooms. (Figure 4). Regulations from the work environment agency did not allow for small double rooms, which is one reason the rooms were large, although they were intended for use by only one patient under normal conditions.

Figure 3. Ward floor plan.

Patient rooms are situated in the outer perimeter with entrance from the outside balcony. Nursing stations, staff rooms, supply rooms, etc., are placed in the inner perimeter.

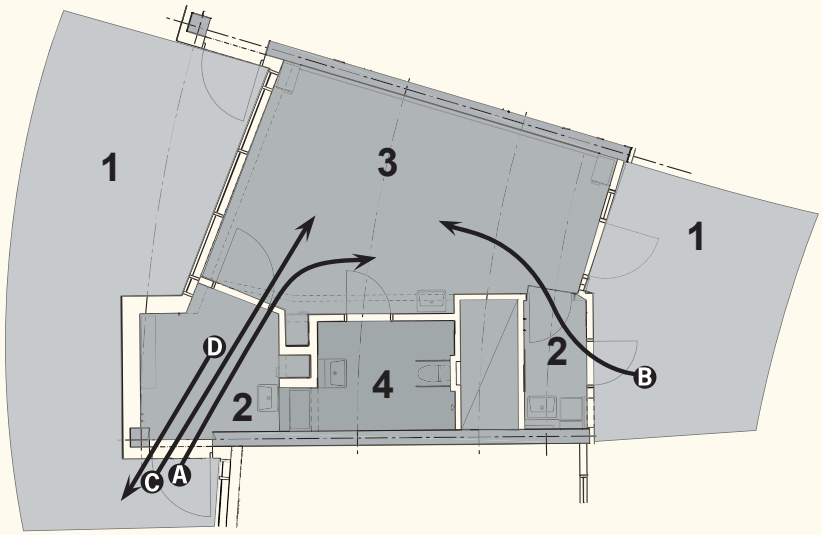


An early simple mock-up, constructed of wood, was located at a university architecture school. A group of experienced staff from the ID department assessed the mock-up under the supervision of university researchers. After this evaluation, some aspects of the patient room unit were corrected or altered. To increase flexibility it was decided to put a door between the patient room and the staff corridor making it possible to bypass the inner anteroom. This door can be used in emergency situations, but also in the event that future users may find the anteroom and the advanced ventilation unnecessary.

At the side of this staff corridor door a window was placed. The window has advantages for the patients, because it is common for isolation patients to feel that they are put aside, neglected, and not seen (Abad et al., 2010; Kirkland, 2009). The window makes it possible for the patient to see staff, but also improves the field of view for the patient. To further enhance communication between patients in isolation rooms and the staff, a voice communication system was installed that can connect with staff telephones.

Figure 4. The patient room with outer and inner anteroom and toilet.

Traffic flows of patients (a), staff (b), relatives (c), and waste (d) are depicted. There is also a door between the patient room and corridor, with a window on side of the door. Ventilation zones (1–4) are marked in the illustration.



It was decided that ceiling-mounted patient lifts should be installed in all rooms. The overhead system makes it possible to lift the patient in different spots of the room (Ulrich et al., 2008).

Sinks and dispensers were placed in anterooms, all patient rooms, and bathrooms. Hand hygiene is the key factor for preventing transmission of hospital-acquired infections. Alcohol-based disinfection is the basis for preventing spread of microbes, but for some agents like *Clostridium difficile* and calici-virus, hand washing is also necessary, because they are not affected by alcohol. The placement and number of alcohol hand rub dispensers has been shown to influence adherence to hand hygiene and therefore was an important design issue (Ulrich et al., 2008).

Flusher-disinfectors were placed in the bathroom in all rooms so that bedpans and other equipment used in patient care would not have to leave the room.

In accordance with the principles of evidence-based design, large windows were provided in each patient room and in staff spaces to allow light and views (Ballard & Rybkowski, 2007; Ulrich, 1984; Ulrich et al., 2008). To ensure patient privacy, including preventing being seen by people circulating on the outside balconies, blinds were built into the windows between the glass panes in the divided windows (Figure 5). Light is of special importance in a northern country like Sweden, since the day period is very short in winter.

Ventilation Requirements

Good evidence or firm recommendations on ventilation standards proved difficult to find, and varied between countries (Beggs et al., 2008; Rydock et al., 2004). The recommendations from the Swedish Association for Infection Control (2010) during the design phase recommended successive negative pressure from corridor to anteroom, and from anteroom to patient room. Leakage of air through walls, ceilings, and floors must be minimized (Rydock et al., 2004; Bartley, Olmstead, & Haas, 2010). Our discussions with Peter Wilson and col-

Figure 5. Window blinds.

The windows are divided in upper and lower parts with separate blinds to ensure privacy control.

leagues in UCLH revealed that national standards in the United Kingdom called for positive pressure in lobbies or anterooms and negative pressure in patient rooms. The CDC's recommendation of 12 air exchanges per hour in rooms for care of tuberculosis is often referred to (CDC, 2005); however, the rationale and evidence supporting this level is unclear.

It was a great help throughout this project that ventilation levels and pressure differences were defined quite early. Early in the project the ID staff members were put in contact with a consultant on ventilation who had much experience in animal laboratories, where requirements are higher than those called for in the ID patient rooms. The consultant strongly recommended that positive pressure in the anterooms would make the system more reliable. Anterooms with positive pressure also become an airlock, minimizing the flow of air and particles from corridor to anteroom, and from patient room to anteroom. The system is appropriate for patients with contagious diseases as well as for immunosuppressed patients. In the final design, the anterooms were ventilated with both incoming and outgoing air. Patient rooms had incoming air only, and the bathroom outgoing air only. The pressure in the anteroom was set at 10 Pa, referred to the inner corridor, and the pressure in patient rooms set to –20 Pa. Temperature could be varied in each patient room from 18°C to 24°C (64°F to 75°F).

The level of air exchanges was set at a normal level of 5 air exchanges per hour. To achieve a high level of safety for the care of patients with airborne transmissible diseases such as tuberculosis, the level could be set at 10 air exchanges per hour. We were convinced that the care taken to minimize air leakage and the prudent use of protective masks could allow a lower level than recommended by the CDC, a level that is not clearly evidence-based.

The high level of 10 air exchanges is technically challenging, and was also planned in combination with a control system for closure of doors. Three levels were defined:

- Level 1: Unlocked doors.
- Level 2: A person must close the door behind them after entering the anteroom to be able to open next door.
- Level 3: Level 2 procedure and the person must wait 30 seconds for the ventilation to be stabilized before opening the door.

Levels of air exchange and door opening can be adjusted on the ward by dedicated staff after decisions from the responsible ID physician.

The building was designed with 17 rooms on each floor. It became evident that the ventilation and door regulation standards were challenging, and it was decided that this level of performance only could be achieved in some rooms on each floor. In the final design, a total of 17 rooms with this high ventilation standard were built, divided among the floors and localized in different parts of the perimeter in order to achieve balance in the ventilation system. These 17 rooms were constructed for HEPA filtration of exhaust air. These rooms are now being

Figure 6. Key system and display.

One key regulates the number of air changes per hour, 1, 5, or 10; one key regulates the electric door lock system with three security levels. The display shows the pressure levels in patient room and anterooms and the settings of the two keys.

modified for HEPA filtration of incoming air because other parts of the hospital are going to be rebuilt or new-built.

Levels of air exchanges and door closure are regulated on the outside of the room by a simple key system. Pressure levels and regulation levels are displayed outside of the room and in a simplified display in nursing stations and work area (see Figure 6).

All other patient rooms were also constructed with negative pressure, although these rooms are not controlled by the same advanced control system. Instead, negative pressure is obtained with controlled the flow of outgoing air.

The obtained ventilation standard is very high and in many aspects fulfilled the needs for high-level isolation units as described by Bannister et al. (2009). As mentioned before, achieving this high level was not a goal at the outset of the project.

Full-Scale Mock-up

Because so many rooms were going to be created that would have advanced technical solutions and installation coordination requirements, building management decided to build a full-scale mock-up with functioning ventilation, water, and sewage, but not gas supply. The mock-up was completed in 2008. For all

parties involved—builders and medical staff users—the mock-up was of great value. In a short period of time more than 125 staff users visited the mock-up room and provided written comments and evaluation. On the basis of the staff evaluations numerous changes were made. Installation coordination was optimized, test pressurizing was performed, and doors were tested and changed.

In scores of discussions between users, planners, and construction personnel, the design and technical solutions were decided on based on the knowledge gained from the mock-up. For example, the ventilation displays and controls were designed through direct dialogue with the medical staff.

Because 50 rooms were going to be built alike, we believe that many mistakes were avoided in completing the patient room units. The mistakes were made and corrected in the mock-up and not duplicated in the real building. Examples of the many issues addressed in the mock-up stage include placement of sinks, alcohol-based hand-rub dispensers, and water closets; type of faucets; height and design of panels; window blinds; placement of equipment in anterooms to maximize space; electrical lighting; and refinement of the patient call system.

Ward

As mentioned, the department was divided into three patient wards on separate floors. The outline of the ward (see Figure 3, above) allowed for circulation for patients and family separate from staff. Patients and relatives enter by the exterior balcony (through outside fresh air) and staff enter by the inner corridor. Working areas receive light from the inner courtyard but also through patients rooms on the corridor (Ulrich et al., 2008).

Mistakes were made and corrected in the mock-up and not duplicated in the real building.

The design dictated that waste would go out of patient rooms via an outer anteroom that opens to the outside balcony. Some supplies enter via the outer anterooms and some are taken to the supply rooms in staff areas.

The shape and the size of the patient room floors, although solving standardization and program requirements, resulted in wards with substantial walking distances for staff, and reduced overview of units from inside corridors. The perimeter of the inner staff corridor is almost 100 meters. A computerized simulation was done to predict factors leading to long walking distances for the staff. Not surprisingly, it was found that the placement of supply rooms, team stations, and rooms for medication preparation were most important. Similar weak spots have been described by others (McCarthy, 2004; Moore, 2011; Ulrich et al., 2008). The solution in this case, similar to one described in 2004, was to decentralize these rooms in order to be closer to staff (Hendrich, Fay, & Sorells, 2004).

Accordingly, two medication preparation rooms were placed on each floor, on opposite sides of the circular units. Supply rooms also were placed on opposing sides of each floor, but simulation of staff walking distances indicated this was not sufficient. Therefore, it was decided that a logistic supply system would be a component of the new facility. Briefly, supplies and laundry are delivered directly

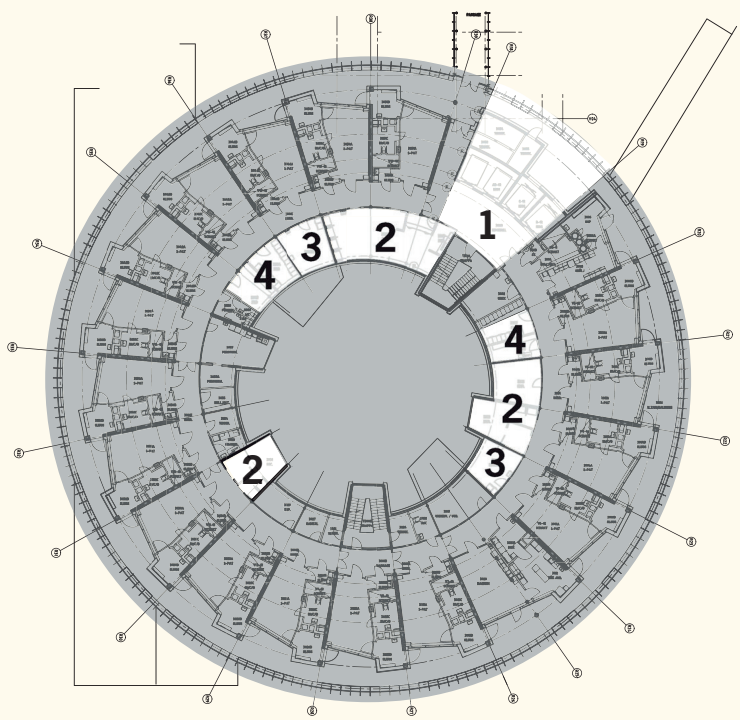
to patient rooms on a 7-days-a-week basis. The logistics system delivers to the supply rooms goods and laundry that are used less frequently 5 days a week. Supplies are delivered by dedicated staff, allowing nurses and nurse assistants more time for nursing and care.

A parallel project was to modify the organization of the clinical staff. There is a strong trend to organize clinical staff in smaller groups, called "patient-focused care" (Inde, 2006). In this way of working, a pair consisting of nurse and nurse assistant serves from five to seven patients in general wards, ideally with one physician attending. A coordinator, who takes all incoming calls and handles contact with relatives and consultants for each patient, is also part of the care system. The team offices were decentralized to three locations on each floor (see Figure 7). A larger staff office was placed at the entrance to each floor, with space for a coordinator and a secretary.

Because medical staff in this facility work almost exclusively with computerized charts and documentation, it was necessary to have many computer terminals

Figure 7. Decentralized offices and rooms.

Illustration of decentralized offices and preparation and store rooms, as well as elevators with access to balcony (1), team offices (2), drug preparation rooms (3), and store rooms (4).



on the wards. In staff offices stations for computer documentation were provided. To support communication all staff members were provided with a cellular phone.

Other rooms included in the inner circle were a break or recreation room for staff; physicians' offices; and a multipurpose room for meetings, education, and rounds. The staff work spaces and break room have abundant daylight from large windows overlooking the inner courtyard of the circular building. In the outer circle on each floor were located a disinfection room, and kitchen and day room or lounge for patients not under isolation measures.

Each floor of patient rooms and staff spaces can be divided into smaller clusters or areas by closing doors in the corridor. These sub-units enable cohorting patients and protecting other patient and staff areas during outbreaks. In such circumstances one patient room can be used as a staff entrance to the sub-unit via the outside balcony.

Patient Flow

A key objective of the new ID facility was to enable proactive separation of patients who have contagious diseases from those who do not (Ulrich & Wilson, 2006; Bartley et al., 2010). This task is most difficult when patients first seek care or enter the hospital. The SARS epidemic showed that spread of disease occurred in waiting areas, such as those in emergency departments, and that hospital-acquired SARS was the most common route of infection in Toronto (Farquharson & Baguley, 2005). The unknown communicable disease is the most difficult to prevent. Because 95% of the inpatients in this ID department are admitted through the emergency room, action has to be taken there to ensure proactive separation of contagious persons and prevent pathogen contamination of interior spaces. The emergency department is a vulnerable entry point, through which outbreaks and epidemics (e.g., influenza and norovirus) often are spread to other patients and inpatient wards.

In response to this challenging problem, the program for the new building required that patient rooms would have exterior (outdoor) entrances not only on the ID floors, but also in the ID outpatient clinic and the emergency department. This goal was achieved by thorough integration and cooperation in the planning and design of the ID department with that of the new emergency department (located on the ground floor below the ID levels). In the final building design, three single rooms with negative pressure and separate exterior (outdoor) entrances were included in the emergency department, allowing for smooth coordination with five similar rooms in the ID department (see Figure 8). Patients coming to the hospital would be directed to these rooms if they have symptoms or risk factors for contagious diseases, as assessed by a physician or ambulance crew (in communication with medical personnel), or as suggested by information in electronic patient records. Ambulances can drive up next to an exterior entrance and bring the patient into their room, preventing the mixing of contagious patients or possible carriers with other patients in waiting areas and treatment spaces.

Based on examination in the emergency department, patients can be transported to an inpatient bed in the ID department on the upper floors using dedicated elevators. From these elevators the patients are moved to their rooms using the exterior balcony as described above. This integrated circulation system makes it possible to transport patients from the emergency room to an ID bed without the risk of contamination or infection transmission to other interior hospital spaces and shared corridors. Design of the exterior balconies led to discussions regarding exposure to wind, rain, and snow, exposure which was unavoidable to some degree. On the other hand, too much enclosure or shelter on the exterior paths could violate the principle that fresh outdoor air reduces infection transmission risk. At the extreme, a high degree of enclosure could produce conditions resembling an indoor corridor. The architect elegantly solved this problem by creating glass lamellae in a 90-degree angle to the outside balconies, providing some shelter to rain, snow and wind but maintaining an outdoor air circulation and climate on the balconies. The lamellae allow window views from patient beds and allow for exposure to natural light.

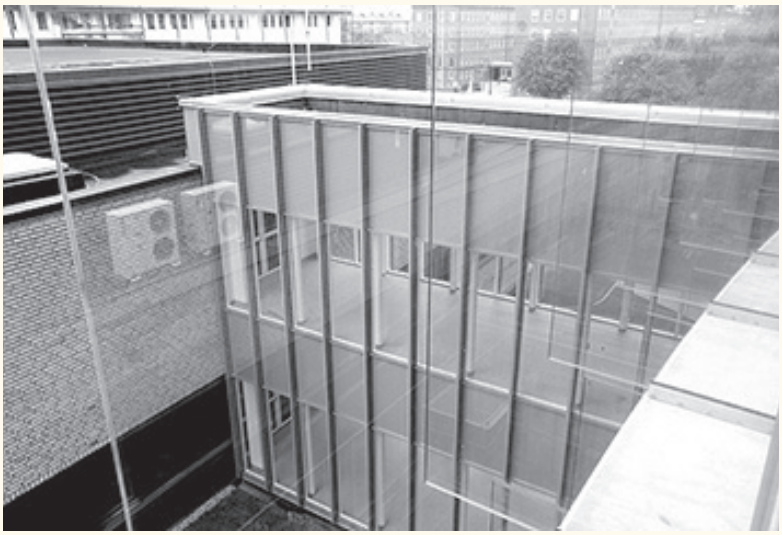
As mentioned earlier, ID patients need to be transported to the ICU, radiology, surgery, and other departments. Walking bridges therefore were created directly from the ID exterior balcony to the ICU and surgery theaters on the first floor (see Figure 9). The distance to surgery is 50–100 meters and to the ICU, 100–150 meters. The next floor has a walking bridge leading to the radiology department and most of the other hospital wards.

Figure 8. Area with isolation rooms.

Area with isolation rooms with entrance from outside both in the emergency department and in the outpatient clinic for infectious diseases. Patients can be transported directly from the examination rooms to the lifts.

Figure 9. Walking bridges.

Walking bridges to other important parts of the hospital. The bridges are separate and short transport ways for contagious patients to, for example, ICU, surgery, and radiology.



Administration, Research, and Education

Because the ID building is part of a university hospital it needed to include rooms for medical and nursing students, education, and research, and small conference areas. These rooms for are located on the two floors above the ID wards. Locating these facilities close to the wards is important and facilitates work in a university hospital, where the staff members are teachers, scientists, and administrators as well as doctors and nurses.

Conclusions

Antimicrobial resistance, emerging ID, healthcare-associated infections, and outbreaks such as pandemic influenza and SARS are realities that highlight the need for giving infection control measures high priority in all hospital design (Bartley et al., 2010; Ulrich et al., 2008; Wilson & Ridgway, 2006; WHO, 2001). This article has described the process for planning and designing a facility tailored for ID in the post-antibiotic era with a high degree of preparedness and flexibility for outbreaks. The flexibility also makes the facility useful for caring for patients who are not infected. Despite the specialized character of the new ID facility we believe that several of the design principles can be generalized to different types of inpatient units, and have relevance for other countries.

First, it is important that the traffic flow or movement of patients with contagious disease is organized to minimize risk for transmission (Ulrich & Wilson, 2006). Emergency departments should have dedicated single rooms with entrance from the outside. The architecture should make it possible to transport patients from these single rooms in the emergency department directly into a room in the ID ward using an exterior balcony or other transport path that minimizes risk of contamination and transmission in interior spaces of the hospital.

Second, echnical solutions, standardization, and evidence-based design make it possible to create a room with high flexibility for use during outbreaks and to help prevent airborne transmissible diseases that also can be used as an ordinary room for everyday care.

Third, anterooms are necessary for stability of systems for a high ventilation standard (Bartley et al., 2010; Rydock et al., 2004; Stockley et al., 2006; Wilson & Ridgway, 2006). In our view anterooms, like single patient rooms, help promote higher hand hygiene compliance (Mertz, Johnstone, Krueger, Brazil, Walter, & Loeb, 2011).

We strongly recommend that staff and other users in hospital projects attend all meetings and become actively engaged in the process.

Standardization of patient rooms is cost-effective and probably fosters higher patient safety. A full-scale mock-up is an effective measure for refining and ensuring the advantages of a standardization and evidence-based design. In this case the mock-up was of great importance for medical staff, architects, planners, and construction personnel.

We support the view that new hospitals should have a high proportion of single rooms. Recently, studies have strengthened the evidence that single rooms reduce acquisition of hospital-associated infections (Teltsch et al., 2011; Hamel, Zoutman, & O'Callaghan, 2011). Other evidence-based advantages have been described in detail by Ulrich et al. (2008).

We strongly recommend that staff and other users in hospital projects attend all meetings and become actively engaged in the process. We would also recommend that building management organize the programming and design process so that involvement of users is encouraged. Our experience has been that the interaction between architect and users is of utmost importance.

Infection control should be a high priority whenever new hospitals are constructed or older facilities are renovated (Bartley et al., 2010; Wilson & Ridgway, 2006). Infection control principles and recommendations should be integrated to a greater degree in guidelines and regulations for healthcare design and construction, and should be reflected in the building contract.

Instead of physical distance, technical solutions—including advanced ventilation systems and outdoor circulation supported by elevators—can enable isolation rooms for infected or contagious patients to be integrated into the main hospital building complex without increasing risk for transmission—far away yet nearby.

Evaluating the New Building: Preliminary Impressions and Evidence

A year after the new facility opened, some preliminary conclusions can be drawn. The flexibility principle led to building large single rooms that could be used as double rooms. The hospital management, which has changed during the year, has decided to use this flexibility not for the proposed seasonal variation or outbreaks but instead to help meet the general shortage of modern patient rooms in our hospital. Thus two of the ID floors currently house 24 patients in 17 rooms, essentially abandoning the single room concept.

The experience of the novel round building is, as noted earlier, that overview is difficult, staff walking distances are longer, and that work processes, supply locations, and offices and nurse stations must be carefully planned and located. The staff-to-patient ratio has remained the same as in the old building, except for the night shift, where a somewhat higher staff-to-patient ratio is needed, due to longer travel distances and less overview. During daytime staffing these factors are overcome by efficient work planning, design, and communication devices.

The principle of transport and entry to patient rooms from the outside balcony has been implemented and works successfully during winter and adverse weather.

The advanced ventilation system works generally well and no problems have surfaced from noise or draft. It has been more difficult for staff to adjust to the door access regulation system with electric locks. Useful and appreciated in tuberculosis care, this door regulation system is more of a hindrance when caring for patients without airborne infection. The doors to ensure adequate air pressure are heavy, and staff complaints have been noted.

Research to establish sound and more detailed evidence for ventilation standards would be of great value for future healthcare projects. The evidence underlying some ventilation standards is unclear and might even be arbitrary. The conclusion from the ID facility is that a high ventilation standard is achievable without excessive cost in a new building. Research to evaluate the new building with respect to patient satisfaction, prevention of healthcare-associated infections, spread of resistant bacteria compared to traditional facilities, and other outcomes, would be of great value.

The most important infection control measure is hand hygiene (Allegranzi & Pittet, 2009). Evidence also points to measures such as avoiding crowding of patients, understaffing, and moving patients around (Borg, Suda, & Scicluna, 2008; Clements, Halton, Graves, Petit, Morton, Looke, & Whitby, 2008; Ulrich et al., 2008). In special cases airborne transmission must be avoided. In our experience optimal patient flow, single rooms, high ventilation standards, and flexibility for isolation are obtainable infection control measures in facility planning.

The main conclusion from our experience both as physicians and as clients actively engaged in the process of creating a new facility is that hospital-acquired infection is such an increasingly important patient safety issue that the design of new facilities for virtually all categories of patients should give utmost priority to infection control.

Implications for Practice

- Infection control measures should be given high priorty in all hospital design.
- Flow or movement of patients with contagious diseases should be organized in ways that minimize the risk for transmission.
- Emergency departments should have single isolation rooms with entrance from the outside. Transport of patients from the ED to ID can be organized outdoors with entrance to the patient's room using an exterior balcony.
- It is possible to design high flexibility patient rooms that are suitable for both a high isolation standard for prevention of airborne diseases and for everyday care.
- Standardization and a full-scale mock-up are effective measures to minimize unnecessary costs and changes during a hospital building process.

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Paper II

ORIGINAL ARTICLE

A Head-to-Head Comparison of Hydrogen Peroxide Vapor and Aerosol Room Decontamination Systems

T. Holmdahl, MD;[1] P. Lanbeck, MD, PhD;[1] M. Wullt, MD, PhD;[1] M. H. Walder, MD, PhD[2]

OBJECTIVE. New technologies have emerged in recent years for the disinfection of hospital rooms and equipment that may not be disinfected adequately using conventional methods. There are several hydrogen peroxide–based area decontamination technologies on the market, but no head-to-head studies have been performed.

DESIGN. We conducted a head-to-head in vitro comparison of a hydrogen peroxide vapor (HPV) system (Bioquell) and an aerosolized hydrogen peroxide (aHP) system (Sterinis).

SETTING. The tests were conducted in a purpose-built 136-m^3 test room.

METHODS. One HPV generator and 2 aHP machines were used, following recommendations of the manufacturers. Three repeated tests were performed for each system. The microbiological efficacy of the 2 systems was tested using 6-log Tyvek-pouched *Geobacillus stearothermophilus* biological indicators (BIs). The indicators were placed at 20 locations in the first test and 14 locations in the subsequent 2 tests for each system.

RESULTS. All BIs were inactivated for the 3 HPV tests, compared with only 10% in the first aHP test and 79% in the other 2 aHP tests. The peak hydrogen peroxide concentration was 338 ppm for HPV and 160 ppm for aHP. The total cycle time (including aeration) was 3 and 3.5 hours for the 3 HPV tests and the 3 aHP tests, respectively. Monitoring around the perimeter of the enclosure with a handheld sensor during tests of both systems did not identify leakage.

CONCLUSION. One HPV generator was more effective than 2 aHP machines for the inactivation of *G. stearothermophilus* BIs, and cycle times were faster for the HPV system.

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A recent editorial called for head-to-head studies comparing hydrogen peroxide vapor (HPV) and aerosolized hydrogen peroxide (aHP) systems, and, to date, none has been published.[1] Therefore, we conducted a study to investigate and compare the efficacy of an HPV system and an aHP system in terms of their ability to inactivate *Geobacillus stearothermophilus* biological indicator (BI) spores distributed around a large single- or dual-occupancy patient room to reflect our intended use.

In Skåne University Hospital (SUS) Malmö, a new infectious disease facility has been built. The facility has 50 standard isolation rooms. These rooms are larger than most single-occupancy hospital rooms and could be used as small double rooms if necessary. In this setting, we are interested in modernizing our hygiene routines and trying new equipment. During the construction phase for our new facility, we built a full-scale mock-up of an isolation room. In this mock-up, new materials and decontamination methods could be tested.

There is now good evidence that contaminated surfaces make a significant contribution to the transmission of nosocomial pathogens, including *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Acinetobacter baumannii*.[2,3] Surfaces in patient areas have frequently been found to be contaminated after conventional cleaning,[4,5] and, linked to these findings, patients admitted to rooms previously occupied by patients positive for VRE, MRSA, *A. baumannii*, and *Pseudomonas aeruginosa* are at increased risk of acquiring these pathogens.[6,7] Given these findings, several area decontamination methods have emerged.[4,8,9] These methods do not rely on the operator to distribute the active substance; thereby, they can achieve coverage of all surfaces in a room and are likely to be more repeatable than conventional methods.

There are 2 commonly used hydrogen peroxide–based methods on the market, the Bioquell HPV system and the Sterinis aHP system.[1,10] These systems have important differences that have been outlined in recent correspon-

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TABLE 1. Biological Indicator (BI) Location and the Number of BIs Inactivated by the Hydrogen Peroxide Vapor (HPV) and Aerosolized Hydrogen Peroxide (aHP) Systems

	HPV			aHP		
Test no.	1	2	3	1	2	3
Main room, top right, near corner	−	−	−	+	−	−
Main room, bottom right, far corner	−	−	−	+	−	+
Main room, top left, far corner	−	−	−	+	−	−
Main room, bottom left, near corner	−	−	−	+	−	−
"In" air lock, top left, near corner	−	−	−	+	+	−
"In" air lock, bottom left, far corner	−	ND	ND	+	ND	ND
"In" air lock, top right, far corner	−	ND	ND	+	ND	ND
"In" air lock, bottom right, near corner	−	ND	ND	+	ND	ND
"In" air lock, bottom right, far corner	ND	−	−	ND	−	−
Bathroom, top left, near corner	−	ND	ND	+	ND	ND
Bathroom, bottom left, far corner	−	ND	ND	+	ND	ND
Bathroom, top right, far corner	−	ND	ND	+	ND	ND
Bathroom, top left, far corner	ND	−	−	ND	+	−
Bathroom, bottom right, near corner	−	−	−	−	−	−
"Out" air lock, top left, near corner	−	ND	ND	+	ND	ND
"Out" air lock, bottom left, far corner	−	ND	ND	+	ND	ND
"Out" air lock, bottom left, near corner	ND	−	−	ND	−	−
"Out" air lock, top right, far corner	−	−	−	+	+	+
"Out" air lock, bottom right, near corner	−	ND	ND	+	ND	ND
"Out" air lock, inside cupboard	−	−	−	+	−	−
Main room, inside cupboard	−	−	−	+	−	−
Back of drawer, open 10 cm	−	−	−	−	−	−
Bathroom, underneath washer/disinfector	−	−	−	+	−	+
Total positive	0	0	0	18	3	3
No. of BIs	20	14	14	20	14	14
% Positive	0	0	0	90	21	21
Control 1	+	+	+	+	+	+
Control 2	+	+	+	+	+	+
Control 3	+	+	+	+	+	+

NOTE. ND, not done.

dence.[10-12] The HPV system generates HPV by adding 35% liquid hydrogen peroxide to a vaporizer heated to 130°C. This produces a vapor, which is distributed in the gas phase until it begins to condense on surfaces in the room.[4,12] After the exposure, an active aeration unit catalyzes the breakdown of HPV to oxygen and water vapor. The HPV achieves a 6-log reduction on bacterial endospores, including *C. difficile*; common hospital bacteria such as MRSA, VRE, and *A. baumannii*; and viruses.[13,14] Surface sampling after HPV shows that it usually eradicates contamination with *C. difficile* and other hospital pathogens.[12,15] Several studies have linked the use of HPV with the control of outbreaks,[16,17] and the use of HPV has been shown to reduce the incidence of *C. difficile* infection.[12]

The aHP system uses pressure to produce an aerosol with a particle size of approximately 8–10 μm from a mixture of 5% hydrogen peroxide, less than 50 ppm silver cations, and less than 50 ppm orthophosphoric acid. After the exposure period, the aerosol is left to decompose passively. The aHP system results in a 4-log reduction of *C. difficile* spores and incomplete inactivation in situ.[8,18] The efficacy of the aHP system against common hospital bacteria such as MRSA and *A. baumannii* has to be fully established. The efficacy against *Mycobacterium tuberculosis* is uncertain.[19,20] The Sterinis system has recently been relaunched as the ASP Glosair system.

METHODS

Description of the Test Facility

The tests were conducted in a 136-m^3 test room in Malmö, Sweden. The area was split into 4 rooms: 2 air locks, a main room, and a bathroom. The area had a dedicated air-handling system that extracted to the outside of the building.

Biological Indicators

The microbiological efficacy of the 2 systems was tested using 6-log Tyvek-pouched *G. stearothermophilus* BIs (Apex Laboratories). The BIs were placed at 20 locations in the first

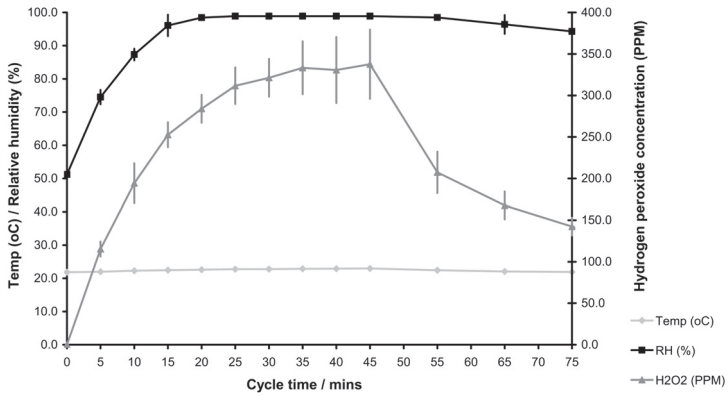

FIGURE 1. Cycle data from 3 hydrogen peroxide vapor cycles. Aggregate data from 3 repeat cycles; error bars represent ±1 SD.

test and 14 locations in the subsequent 2 tests for each system. BIs were located in the main room, the bathroom, the air locks in opposing high and low corner locations, and several challenging locations, such as inside cupboards and drawers, to test the distribution of the systems (see Table 1 for specific BI locations). After exposure to either HPV or aHP, the BIs were transferred into tryptone soya broth, incubated, and read according to the manufacturer's instructions.

Decontamination Equipment and Configuration

Two aHP machines were used, following recommendations of the manufacturer (Sterinis). The 2 generators were placed in the center of the main room, and external doors were sealed using adhesive tape. The concentration of hydrogen peroxide was measured by a Draegar sensor (Polytron 7000) inside the enclosure. For each of the 3 tests, 3 back-to-back injections of 6 mL/m^3 hydrogen peroxide were performed. Aeration was assisted using the air-handling system. The test was considered ended when the readings on the handheld sensor were less than or equal to 1 ppm in the air lock and less than or equal to 2 ppm at any point in the room. (The Health and Safety limit for hydrogen peroxide exposure in Sweden is 1 ppm for a working day or 2 ppm for 15-minute period.)[21]

One Bioquell Q10 suite was used, following recommendations of the manufacturer. The HPV generator (Q10) was placed in the center of the main room, the R10 (aeration unit) was placed in the doorway of the main room air lock, oscillating pedestal fans were placed in the doorway of the bathroom and the other air lock, and the control pedestal was placed outside the door of the main room. External doors were sealed using adhesive tape, and the handheld sensor was used to monitor for leakage periodically. The concentrations of hydrogen peroxide, temperature, and relative humidity in the room were monitored by the Q10, and readings were recorded every 5 minutes during the injection phases and regularly during aeration (the removal of HPV). For the 3 tests, 900 mL of hydrogen peroxide was injected, with 30 minutes dwell, which equates to approximately 6.6 g/m^3. Aeration was assisted using the air-handling system. The test was considered ended when the readings on the handheld sensor were less than or equal to 1 ppm in the air lock and less than or equal to 2 ppm at any point in the room.

RESULTS

Data from the HPV cycles are presented in Figure 1. The increase and plateau in relative humidity and HPV concentration are consistent with the saturation of the air with hydrogen peroxide and subsequent condensation onto surfaces.[22] The peak hydrogen peroxide concentration was 338 ppm. The total cycle time (including aeration) for the 3 HPV tests was 3 hours. All BIs were inactivated in each of the 3 tests (Table 1).

The hydrogen peroxide concentration from the aHP tests is presented in Figure 2. The tests were performed sequentially on the same day, and it appears that there was an accumulation of hydrogen peroxide in the enclosure because the peak hydrogen peroxide concentration increased from less than 100 ppm in the first test to approximately 130 ppm in the second test and to greater than 150 ppm in the third test. Ten percent of BIs were inactivated in the first test, compared with 79% in the second and third tests (Table 1). Total cycle times were approximately 3.5 hours.

Monitoring around the perimeter of the enclosure with a handheld sensor during tests did not identify leakage for either system.

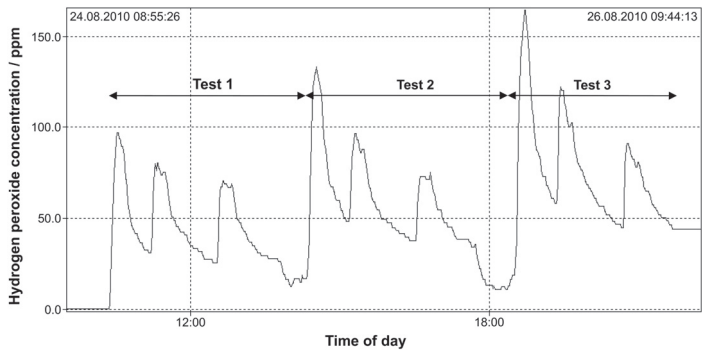

FIGURE 2. Hydrogen peroxide concentration from the 3 aerosolized hydrogen peroxide tests.

DISCUSSION

Hydrogen peroxide is a potent disinfectant and sterilant that penetrates the bacterial cell wall by passive diffusion and then acts by denaturing proteins, DNA, and other components inside the bacterial cell.[23] It is not harmful to the environment because it breaks down to water and oxygen, leaving no toxic by-products. We consider hydrogen peroxide decontamination an important method in terminal disinfection of rooms previously occupied by patients positive for MRSA, VRE, *Acinetobacter* spp., *C. difficile*, or other problem bacteria.

We tested 2 different types of hydrogen peroxide–based whole-room decontamination systems. The main difference between the 2 technologies is the formation of the HPV or aerosol. HPV creates a vapor in gaseous form from 35% w/w hydrogen peroxide, whereas aHP creates an aerosol from 5% hydrogen peroxide, with drops of 8–10 μm. The aHP aerosol is stabilized using silver ions and other chemicals to avoid aggregation before the drops reach the target. Other differences between the 2 systems are the peak hydrogen peroxide concentration, which is twice as high in HPV as in aHP, and the total hydrogen peroxide concentration (measured as area under the curve), which is higher for HPV.

Bacterial endospore BIs are typically used to monitor the effectiveness of sterilization and high-level disinfection procedures, such as autoclaves and vapor-phase decontamination methods.[24] In our study, the HPV system inactivated BIs at all locations in each of the 3 tests, suggesting a homogenous and repeatable distribution. BIs are used routinely to monitor HPV decontamination systems.[4,12,22]

Several studies have used BIs to monitor aHP systems. After 3 back-to-back cycles, 13% of 146 BIs grew in hospital rooms in 1 study, although 3 cycles inactivated all BIs in separate experiments in 22 rooms in a surgery department and inside ambulances.[25] In this study, 1 or 2 cycles had little impact on the BIs. Therefore, we chose to use 3 back-to-back cycles for each test of the aHP machine. However, even after 3 back-to-back cycles were used, the aHP system inactivated only 10% of BIs on the first test and 79% of BIs on the subsequent tests. According to the manufacturer, the failure in decontamination in the first aHP test was probably a result of miscalculation of air humidity, which should be done automatically by the system. This was corrected by the machine for the following tests. Even with optimal function, the aHP system failed to inactivate 3 of 14 BIs in the second and third tests. The BIs that grew were not always in the same location, suggesting that the distribution was not consistent between tests.

One conclusion of our study can be that a higher hydrogen peroxide concentration during a longer time is superior for achieving disinfection.

One HPV generator was used, but 2 aHP machines were used. Despite this, the HPV system was more effective for the inactivation of BIs and produced a shorter total cycle time (3 vs 3.5 hours). Turnaround time is a crucial component of vapor-phase disinfection technologies. Several recent studies have used a single cycle rather than the 3 back-to-back cycles that we used for the aHP system.[8,18] The use of 1 cycle for the aHP system would have reduced the total cycle time but would have further reduced the microbiological impact of the system; on the basis of the results from Andersen et al,[25] it is unlikely that any BIs could have been inactivated using fewer than 3 cycles.

The peak concentration of HPV (338 ppm) and other cycle parameters such as changes in relative humidity during the HPV cycles are consistent with the findings of others.[4,22] However, the concentration of hydrogen peroxide identified in the aHP tests was higher than that in other studies. For example, 1 study recorded hydrogen peroxide concentration peaks of 2–60 ppm[23] and another 43–114 ppm,[19] compared with greater than 150 ppm in our study. Given the higher concentration of liquid hydrogen peroxide used in the HPV system (35% vs 5%), the higher concentration of hydrogen per-

oxide measured in the air when using the HPV system is not surprising. Hydrogen peroxide sensors differ in their performance,[26] and since 2 different types of sensor were used, it is not possible to compare these values accurately and directly.

The aim of this study was not to measure whether there was any corrosive activity attributable to either of the systems. There are no reports on this important question in the literature. It is possible that the residues of silver ions left after the aHP cycle are problematic in the environment because silver exposure is known to trigger resistance in bacteria.[27]

Since hydrogen peroxide reaches levels that would be toxic for patients and staff during decontamination with both the HPV and aHP systems, ventilation and doors have to be sealed during treatment. It is also important that the process is monitored and handled by specially trained and experienced staff. In hospitals with a high prevalence of these bacteria, it might be rational for departments to own their equipment, to train dedicated persons of their staff, and to run disinfection cycles on a regular basis. In low-prevalence hospitals, it might be more rational to hire the equipment only for outbreak situations.

Our study has showed that 1 HPV system was more effective than 2 aHP systems for the inactivation of *G. stearothermophilus* BIs and that cycles were faster for the HPV system. Since the data suggesting a clinical impact relate to the HPV system and not to the aHP system, the aHP system lacks published in vitro efficacy against key nosocomial bacteria (especially the catalase-positive bacteria[13]), and on the basis of the results of our study, the HPV system was superior in our setting.

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Paper III

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY MAY 2016, VOL. 37, NO. 5

ORIGINAL ARTICLE

Hydrogen Peroxide Vapor Decontamination in a Patient Room Using Feline Calicivirus and Murine Norovirus as Surrogate Markers for Human Norovirus

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OBJECTIVE. To determine whether hydrogen peroxide vapor (HPV) could be used to decontaminate caliciviruses from surfaces in a patient room.

DESIGN. Feline calicivirus (FCV) and murine norovirus (MNV) were used as surrogate viability markers to mimic the noncultivable human norovirus. Cell culture supernatants of FCV and MNV were dried in triplicate 35-mm wells of 6-well plastic plates. These plates were placed in various positions in a nonoccupied patient room that was subsequently exposed to HPV. Control plates were positioned in a similar room but were never exposed to HPV.

METHODS. Virucidal activity was measured in cell culture by reduction in 50% tissue culture infective dose titer for FCV and by both 50% tissue culture infective dose titer and plaque reduction for MNV.

RESULTS. Neither viable FCV nor viable MNV could be detected in the test room after HPV treatment. At least 3.65 log reduction for FCV and at least 3.67 log reduction for MNV were found by 50% tissue culture infective dose. With plaque assay, measurable reduction for MNV was at least 2.85 log units.

CONCLUSIONS. The successful inactivation of both surrogate viruses indicates that HPV could be a useful tool for surface decontamination of a patient room contaminated by norovirus. Hence nosocomial spread to subsequent patients can be avoided.

Infect Control Hosp Epidemiol 2016;37:561–566

In recent years, recurrent norovirus outbreaks have emerged as challenging infections that cause closing of wards. Noroviruses are highly infectious and shed in high concentrations in feces and vomitus. They are spreading by the fecal-oral route, from hand to hand contact, by aerosol, [1–4] and by contaminated food and water.[5–7] These stable viruses can persist on contaminated surfaces for long periods.[4,8]

Noroviruses include 5 genogroups; 3 of them (I, II, and IV) infect humans, whereas norovirus genogroup III infects cattle and genogroup V, the murine norovirus (MNV), infects mice. The human and murine noroviruses infect and are shed via the gastrointestinal tract, whereas another calicivirus, feline calicivirus (FCV), infects the respiratory tract. Human noroviruses do not grow in cell culture while MNV and FCV grow in murine and feline cells, respectively. This makes MNV and FCV models suitable for virus growth and viability studies. FCV has been used in several inactivation studies of disinfectants.[9,10] More recently the focus has moved toward MNV since its route of transmission resembles more transmission of human norovirus.[11,12]

Methods to inactivate noroviruses need to take into account that they are nonenveloped and hence resistant to alcohol and lipid-destroying disinfectants.[13] Epidemiologic data suggest that viable norovirus can persist after manual environmental cleaning and disinfection even with bleach, which is the disinfectant recommended for surfaces.[13]

Hydrogen peroxide vapor (HPV) distribution systems are independent of employees distributing fluid disinfectants and therefore more repeatable than conventional cleaning.

HPV has been shown to achieve a 6-log reduction on bacterial endospores,[14] including *Clostridium difficile*, common hospital bacteria such as methicillin-resistant *Staphylococcus aureus*,[15] vancomycin-resistant *Enterococcus*, and *Acinetobacter baumannii*.[16] There are strong indications from clinical practice that HPV disinfection can reduce the frequency of outbreaks with bacterial infections and terminate them.[17–22]

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HPV also has a documented virucidal activity shown against several enteric and respiratory viruses, including adenovirus, poliovirus, rotavirus, MNV, and FCV.[12,23–25] However, most of these virucidal data have been acquired in test boxes and not in full-scale ward rooms.

The purpose of our study was to determine whether HPV can be used to decontaminate surfaces in a patient room from caliciviruses. We therefore dried both FCV and MNV on plastic surfaces, which were then exposed to HPV, and we determined the fraction of viable virus that could be recovered.

METHODS

Virus, Cells, and Media

FCV (strain 2280 [ATCC VR-2057]) and a feline permissive fetal cell line (FCWF) were gifts from Anna Lindhe from the Veterinary Faculty of Uppsala University, Uppsala, Sweden. FCWF cells were grown in Dulbecco minimum essential medium with high glucose and pyruvate (catalog no. 41966029, Life Technologies). Cells were grown in 10% fetal calf serum (FCS; Life Technologies), supplemented with 5% penicillin/streptomycin.

MNV (strain Berlin/06/06/DE S99) and a permissive murine cell line (RAW 264.7) were gifts from Maren Eggers and Gisela Enders, MVZ GbR Virologie, Stuttgart, Germany. The RAW cells were grown in Dulbecco minimum essential medium (no pyruvate; catalog no. FG 0435, Biochrom), with 10% low endotoxin FCS (catalog no. A15-102, PAA Laboratories; or Hyclone FBS, Nordic Biolabs), supplemented with 1% nonessential amino acids and 5% penicillin/streptomycin.

All cell growth plastic material (6- and 96-well plates and flasks) was from Corning Life Sciences.

Virus Stocks

For FCV, 3 bottles of the FCWF cells (each bottle with a 25-cm^2 growth area) were grown to 80%–90% confluence. The medium was removed and 200 μL of virus inoculum was added to 1 mL of the cell medium and incubated for 2 hours at 37°C in 5% CO_2. The inoculum was then removed and fresh medium was added. All supernatant material harvested by 48 hours was clarified by centrifugation at 2,000 *g* for 5 minutes and treated by ultracentrifugation at 39,000 *g* for 1 hour to concentrate the viral stock. Stock solution was aliquoted and stored at −70°C.

For MNV, 3 bottles of the RAW 264.7 cells (each bottle with a 25-cm^2 growth area) were grown to 80%–90% confluence. The medium was removed and 500 μL of virus inoculum was placed on the naked cells and incubated for 1 hour at 37°C in 5% CO_2. The inoculum was then removed and fresh medium was added. After 5 days a complete cytopathic effect was observed and the medium was harvested. The cells were removed by centrifugation at 2,000 *g* for 5 minutes and the clarified supernatant aliquoted and stored at −70°C.

Determination of 50% Tissue Culture Infective Dose (TCID50)

Test material was serially diluted in medium in 10-fold steps and transferred to 96-well microtiter plates where cells had reached approximately 90% confluence. The cytopathic effect was observed with an inverse light microscope and used for calculation of which 50% of wells were infected (TCID50) as described by Reed and Muench.[26] Viral titers were expressed in 10logs of TCID50 units/100 μL of inoculum.

Plaque Assay

Target cells (1.5 million cells/mL) were seeded into 6-well plates with well diameters of 35 mm and grown to 80%–90% confluence. After removing the medium and washing the cells with fresh medium, 100-μL 10log dilutions of virus, containing test material diluted with 100 μL of medium to cover all cells, were added to wells in duplicate. Following incubation for 1 hour at 37°C, medium was removed and replaced with 2 mL/well of fresh medium with 1.5% low melting point Seaplaque agarose (FMC Bioproducts) at 37°C and left to solidify. The plates were kept in a humidified incubator with 5% CO_2 at 37°C.

After 2 days the plates were fixed with 10% formaldehyde added on top of the gel for 30 minutes. The gels were then gently removed and the cell layer stained with crystal blue to facilitate the viral plaque counting. Virus titers were calculated as the mean of plaque-forming units/100 μL of inoculum of duplicate wells and were expressed in 10log units.

Preparation of Contaminated Plastic Surfaces for Exposure to HPV

Next, 100 μL of virus stock was spread out thinly in triplicate around the centers of three 35-mm wells in 6-well plates and allowed to dry at room temperature in a hood. When completely dried after 2 hours the plates were stored at −70°C until used.

On the day of experiment the plates were placed in the test rooms as described below.

Reference Biological Indicators (BIs)

For control of the HPV efficacy, 6-log Tyvek-pouched *Geobacillus stearothermophilus* BIs (Apex Laboratories) were placed in duplicate adjacent to each virus test plate. After each HPV test run, the BIs were transferred into tryptone soya broth, incubated, and read according to the manufacturer´s instructions as earlier described.[14]

Test Facility

The HPV exposure test was performed in a nonoccupied patient room consisting of a main single bedroom and its attached bathroom (Figure 1a). The bedroom contained a bed with mattress, a bed table, and a chair with fabric. (Equipment, including fabric, can remain in a room during HPV treatment.) A similar unit was used as an HPV-unexposed control

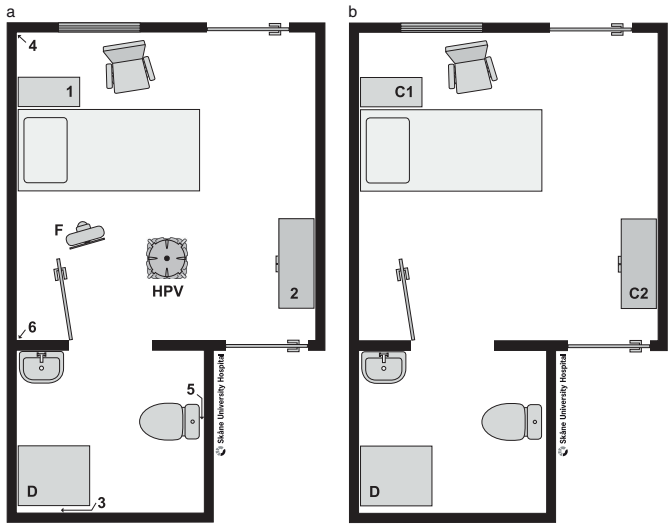

FIGURE 1. a. Test room. Single bed patient room (3.4 m × 3.3 m × 3.9 m) with en suite bathroom (1.9 m × 2.0 m × 2.2 m). D, flusher disinfector; F, pedestal fan; HPV, hydrogen peroxide vapor (Bioquel Q10) with attached aeration unit. Sample locations are indicated by numbers: 1. Main room, on a table by the bed. 2. Main room, high up on linen cupboard. 3. Bathroom, behind flusher. 4. Main room, floor in a corner. 5. Bathroom, behind toilet. 6. Main room, floor behind door in a corner. b. Control room. Sample locations: C1, Main room, on table by the bed, C2. Main room, high up on linen cupboard.

room (Figure 1b). The ward had a dedicated air-handling system to the outside of the building, and it was used to enhance removal of HPV.

Design of Experiments

Dried FCV and MNV were tested in separate experiments. At each test run three 35-mm diameter wells were used at each position and each HPV exposure experiment was repeated on 3 occasions. Virus plate/BI combinations were placed at mid-height, high up, and close to the floor at 6 positions, including challenging positions such as on top of a linen cupboard and behind the decontamination apparatus (Figure 1a).

At each exposure experiment, the HPV-untreated patient room was used to determine virus recovery without HPV and as the basis for calculating the reduction of infectivity by HPV. Two control plate/BI sets, prepared as above, were used and positioned as shown (Figure 1b).

The lowest measurable titer was defined as detection limit multiplied by the dilution factor.

The HPV was generated by a Bioquell Q10 Suite system (Bioquell) following the recommendations of the manufacturer. Both the HPV generator and its attached HPV aeration unit were placed in the center of the room. Owing to pretest results with BIs, where we had indications that the high ceiling (3.9 m) in the ward room was giving complicated aerodynamics, we included an oscillating pedestal fan in front of the doorway of the bathroom to enhance a homogenous distribution of HPV. The Bioquell control/monitoring unit was placed in the corridor, outside the unit. During HPV exposure, the doors to the test unit were sealed using adhesive tape. A hand-held sensor was used to monitor for leakage periodically since HPV at peak treatment concentrations is highly toxic.

The concentration of hydrogen peroxide in the test room was recorded every 5 minutes during the injection phase. The test room was considered safe for entry when the concentration was less than or equal to 1 ppm.

RESULTS

HPV Profiles

In the experiments presented here we had a gassing time of 40–50 minutes and a dwell time of 15 minutes before the degradation started. We reached a peak between 474 and 505 ppm. The total cycle time was approximately 3 hours. This is similar to typical profiles reported previously.[14]

Inactivation of FCV

No viable FCV was recovered from any of the triplicate wells at any position in the treated room in any of the 3 test runs.

TABLE 1. Feline Calicivirus Inactivation by Hydrogen Peroxide Vapor (HPV) in 3 Separate Experiments (A, B, C)

No.	Position		Log TCID50/100 µL (from wells 1/2/3)[a]	BIs
1	Main room, on bed table	A	≤1.0	neg
		B	≤1.0	neg
		C	≤1.0	neg
2	Main room high up on linen cupboard	A	≤1.0	neg
		B	≤1.0	neg
		C	≤1.0	neg
3	Bathroom behind flushing disinfector	A	≤1.0	neg
		B	≤1.0	neg
		C	≤1.0	neg
4	Main room bottom corner	A	≤1.0	neg
		B	≤1.0	neg
		C	≤1.0	neg
5	Bathroom behind toilet	A	≤1.0	neg
		B	≤1.0	neg
		C	≤1.0	neg
6	Main room down left behind door	A	≤1.0	neg
		B	≤1.0	neg
		C	≤1.0	neg
C1	Control room on bed table	A	4.5	pos
		B	5.0	pos
		C	4.5	pos
C2	Control room high up on linen cupboard	A	4.5	pos
		B	4.7	pos
		C	4.7	pos
	Mean recovered FCV titer in untreated controls TCID50/100 µL		4.65	
	Reduction of infectivity[b]		≥3.65 log units	

NOTE. BI, biological indicator; FCV, feline calicivirus; TCID50, 50% tissue culture infective dose.
[a]In each experiment, the mean of triplicate wells (1/2/3) is shown.
[b]Calculated by subtracting lowest measurable titer (here ≤1.0) from mean titer of untreated controls.

As expected, FCV grew from all triplicate wells at each position in the untreated room in all 3 test runs.

As shown in Table 1 we could document a reduction of infectivity of at least 3.65 logs by TCID50, calculated by subtracting lowest measurable titer (here ≤ 1.0) from 4.65, the mean titer of untreated controls.

Inactivation of MNV

The MNV was measured with both TCID50 and plaque test. No viable MNV was recovered from any position in the treated room in any of the 3 test runs. Virus grew in all triplicate wells in the untreated room in all 3 test runs.

The MNV grew at 4.67 log as measured by TCID50 in the untreated room. Thus we could document a reduction of infectivity of at least 3.67 logs as measured with TCID50 since the lowest measurable titer was less than or equal to 1.0. In parallel, by plaque assay we could document at least 2.85 log reduction, calculated by subtracting the lowest measurable titer (≤0.5) from the mean titer of untreated controls (Table 2).

Inactivation of BIs

Duplicate BIs were tested at each of the 6 positions during the 3 test runs with FCV and 3 test runs with MNV; altogether, 72 BIs were used. In the HPV-treated room, BIs were negative with few exceptions. In 1 test run (with MNV), both spore BIs at the same challenging position (down low and behind an opened door) became positive. In the HPV-untreated room all the BIs were positive, as expected.

DISCUSSION

Several agents used to decontaminate surfaces from nonenveloped viruses, such as chlorine and aldehydes, both are toxic and leave toxic deposits after treatment. Hydrogen peroxide degrades into water and oxygen and has thereby the advantage of leaving no toxic traces.

Since HPV efficacy can be reduced by an excess of organic substances, manual cleaning to eliminate visible dirt always has to be performed before applying hydrogen peroxide.

Our findings confirm the data obtained by Tuladhar et al,[12] who used an isolator for MNV and a nonhospital test room for poliovirus. They tested several viruses dried on stainless steel, framing panel carriers, and gauze carriers, whereas we used 2 caliciviruses (FCV and MNV) and dried both on plastic labware.

We used a patient room that included fabric material as a test room to make the trial as realistic as possible (Figure 1a).

TABLE 2. Murine Norovirus Inactivation by Hydrogen Peroxide Vapor (HPV) in 3 Separate Experiments (A, B, C)

No.	Position		Log TCID50/ 100 µL (wells1/2/3)[a]	Log PFU/ 100 µL (wells1/2/3)	BIs
1	Main room, on bed table	A	≤1.0	≤0.5	neg/neg
		B	≤1.0	≤0.5	neg/neg
		C	≤1.0	≤0.5	neg/neg
2	Main room, high up on linen cupboard	A	≤1.0	≤0.5	neg/neg
		B	≤1.0	≤0.5	neg/neg
		C	≤1.0	≤0.5	neg/neg
3	Bathroom, behind flushing disinfector	A	≤1.0	≤0.5	neg/neg
		B	≤1.0	≤0.5	neg/neg
		C	≤1.0	≤0.5	neg/neg
4	Main room, right low	A	≤1.0	≤0.5	neg/neg
		B	≤1.0	≤0.5	neg/neg
		C	≤1.0	≤0.5	neg/neg
5	Bathroom, behind toilet	A	≤1.0	≤0.5	neg/neg
		B	≤1.0	≤0.5	neg/neg
		C	≤1.0	≤0.5	neg/neg
6	Main room, down left behind door	A	≤1.0	≤0.5	neg/neg
		B	≤1.0	≤0.5	neg/neg
		C	≤1.0	≤0.5	pos/pos
C1	Control room, on bed table	A	4.75	3.3	pos/pos
		B	5.25	3.5	pos/pos
		C	4.5	3.8	pos/pos
C2	Control room, up on linen cupboard	A	4.25	3.0	pos/pos
		B	3.5	3.5	pos/pos
		C	5.5	3.0	pos/pos
	Mean titer of untreated controls		4.67	3.35	
	Reduction of MNV infectivity[b]		>3.67 log units	>2.85 log units	

NOTE. BI, biological indicator; MNV, murine norovirus; PFU, plaque-forming units; TCID50, 50% tissue culture infective dose.

[a]In each experiment, the mean of triplicate wells (1/2/3) is shown.

[b]Calculated by subtracting lowest measurable titer (here ≤1.0 for TCID50 and ≤0.5 for plaque test) from mean titer of untreated controls.

The viruses and the BIs were placed together in challenging positions.

All 72 BIs except 2 at the same position in a single run became negative, indicating a generally good and even distribution of the HPV. The 2 positive BIs were positioned behind a door and in that run the pedestal fan was accidentally directed in a suboptimal direction. In spite of this the corresponding virus tests showed inactivation. Endospores are considered to be more difficult to inactivate than viruses. If a room is not rectangular (eg, en suite in configuration as in our test), we recommend to do a pretest with BIs and if they indicate problems with HPV distribution, a fan directed towards the area with suboptimal distribution of HPV can be used.

We did not in any case recover virus at any HPV-treated position.

The experiments were designed to study virus that had dried completely in 35-mm wells and hence our input inoculum volume was restricted to 100 µL/well; greater volumes can cause a thicker rim deposit around the well bottom edge. This volume is a limitation since our multistep procedure (drying, storage of plates at −70°C, exposure with/without HPV at room temperature for hours, recovery, renewed storage at −70°C, and finally infectivity titrations) did not allow for measuring a reduction of more than 3–4 logs.

In conclusion, our inactivation data from both our viruses, in particular MNV, the closest related to human noroviruses, indicate that HPV could be used to avoid nosocomial spread of human norovirus in clinical settings where the environment has been contaminated.

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Paper IV