

2 HEALTHCARE-ASSOCIATED INFECTIONS

2.1 INTRODUCTION AND DEFINITION

Healthcare-associated infections (HCAI) are infections occurring after exposure to healthcare, often, but not always, as a consequence of this exposure. Hospital-acquired infections (HAI), also referred to as ‘nosocomial infections’ (NI) or simply ‘hospital infections’, are infections occurring during a stay in hospital that were neither present nor incubating at the time of hospital admission^{1,2}. Mostly, nosocomial infections only appear in patients hospitalised for 48 hours or longer, which resulted in the use of the 48-hours criterion in several epidemiological surveillance systems. Friedman et al. have proposed HCAI as a distinct category defined as ‘infections occurring in patients at the time of hospital admission or within 48 hours of admission if the patient received specific home care (such as intravenous therapy, wound care or specialised nursing care) or attended a hospital or haemodialysis clinic in the 30 days before the infection, if the patient was hospitalised two or more days in the 90 days before infection or if he or she resided in a nursing home or long-term care facility’³. The latter group of infections are often referred to as nursing home-acquired infections and long-term care-acquired infections^{4,5,6}. Community-acquired infections are infections in patients not meeting any of the above criteria, and therefore, although one may find many examples to the contrary in scientific literature, they do not include nursing home-acquired infections. In the following text, we will follow the concepts introduced by Friedman et al. although the

term ‘health care-associated infections’ will encompass hospital-acquired (nosocomial), nursing home-acquired, long-term care-associated, outpatient care-associated (e.g. dialysis, chemotherapy) and finally home care-associated infections.

Finally, it should be noted that further difficulties emerge in defining unequivocal subcategories of healthcare-associated infections because the way healthcare services are organised reflects the country-specific division of labour between healthcare providers, which is becoming increasingly complex in many countries. It is a commonly observed phenomenon that institutions with similar names such as ‘general hospital’, ‘acute hospital’, and ‘psychiatric hospital’ often do not perform identical roles in different healthcare systems⁷. Similarly, the term ‘nursing home’ may or may not include residential care for the elderly.

2.2 EPIDEMIOLOGY OF HEALTHCARE-ASSOCIATED INFECTIONS

The incidence of healthcare-associated infections varies by body site and is determined to a large extent by underlying disease conditions in the patients and their exposure to high risk medical interventions, such as surgical procedures and invasive devices.

National or multicentre point prevalence surveys of nosocomial infections performed in industrialised countries in recent years have shown that the percentage of patients

Table 2.2.1. Overview of recent prevalence surveys of nosocomial infections in industrialised countries

	NI Prevalence	Reference	Hospitals (N)	Patients (N)
UK, 1996	9.0%	8,9	157	37 111
Germany, 1997	3.5%	10	72	14 996
France, 2001 (1996)	6.6%	11,12	1 533	162 220
Switzerland, 2002	8.1%	13,14	60	7 540
Greece, 2000	9.3%	15	14	3 925
Italy, Lombardy, 2000	4.9%	16	88	18 667
Slovenia, 2001	4.6%	17	19	6 695
Canada, 2002	10.5%	18	25	5 750
Italy, INF-NOS, 2002	7.5%	19	15	2 165
Portugal, 2003	8.4%	20	67	16 373
Denmark, 2003	8.7%	21	38	4 226
Latvia, 2003	3.9%	22	7	3 150
Finland, 2005	8.5%	23	30	8 234
Sweden, 2004–2006 ^(a)	9.5%	24	56	13 999
UK and Ireland, 2006	7.6%	25	273	75 763
France, 2006 ^(b)	5.0%	26,27	2 337	358 353
Norway, 2002–2007 ^{(a)(c)}	6.8%	28,29,30	53	11 359
Scotland, 2007	9.5%	31	45	11 608
Spain, (1990–) 2004–2007 ^(a)	6.8%	32,33,34	259	58 892
Lithuania, 2003,2005,2007 ^(a)	3.7%	35,36	35	8 000
Netherlands, 2007	6.9%	37	30	8 424
Mean	7.1%			

(a) Average numbers from repeated point prevalence surveys in several years.

(b) Figure for acute care facilities only.

(c) Corrected for non-included infection types (i.e. those other than UTI, LRTI, SSI and BSI).

with a nosocomial infection on any given day in acute care hospitals is on average 7.1%, ranging from 3.5% to 10.5% (Table 2.2.1).

The main infection sites and the average percentage they represent of the total of nosocomial infections in this series of prevalence studies were urinary tract infections

(27%), lower respiratory tract infections including pneumonia (24%), surgical site infections (17%) and bloodstream infections (10.5%). The remaining infection sites represent on average 19.3% of the prevalence survey overview and include gastrointestinal infections (mainly *Clostridium difficile* infection (CDI)), skin and soft tissue infections, central nervous system infec-

tions, etc. Globally, the relative frequency figures compare well with figures from the hospital-wide component of the National Nosocomial Infections Surveillance System (NNIS) of the US Centres for Disease Control (1990–1992)³⁸.

Micro-organisms in healthcare-associated infections

Figure 2.2.1 shows the distribution of the most frequently isolated micro-organisms in all infection sites in those national prevalence surveys that recorded this information.

Overall, *Escherichia coli* and *Staphylococcus aureus* are the most frequently involved, followed by *Pseudomonas aeruginosa*, *Enterococcus spp.*, coagulase-negative staphylococci, *Candida spp.*, other Enterobacteriaceae such as *Klebsiella spp.* and *Enterobacter spp.* *Clostridium difficile* has become more prominent in recent years due to the epidemic of the more virulent NAP I ribotype 027 strain in the US, Canada and some EU countries^{39,40,41,42,43,44}.

As well as these most commonly occurring pathogens, a small proportion (less

than 10%) of nosocomial infections occur in the context of nosocomial outbreaks^{45,46}. As documented by recent review studies of nosocomial outbreaks^{47,48,49}, the most frequently involved micro-organisms in reported outbreaks are those causing endemic infections such as *S. aureus* (14% of reported outbreaks), *P. aeruginosa* (8%), *Klebsiella pneumoniae* (7%), *Acinetobacter spp.* (7%) and *Serratia spp.* (6%), but also other micro-organisms such as *Salmonella spp.* (4%), *Legionella pneumophila* (3%), *Aspergillus spp.* (2%), hepatitis virus (10% of total, of which HBV 48%, HCV 34%, HAV 18%), norovirus (2%), influenza/parainfluenza (2%), rotavirus (2%), adenovirus (1%) and of course SARS coronavirus (obviously over-represented in scientific literature). Outbreaks that led to significantly more frequent closures of the affected medical departments were caused by norovirus (closure rate 44%), influenza/parainfluenza virus (39%), (group A) Streptococci (29%) and *Acinetobacter spp.* (23%).

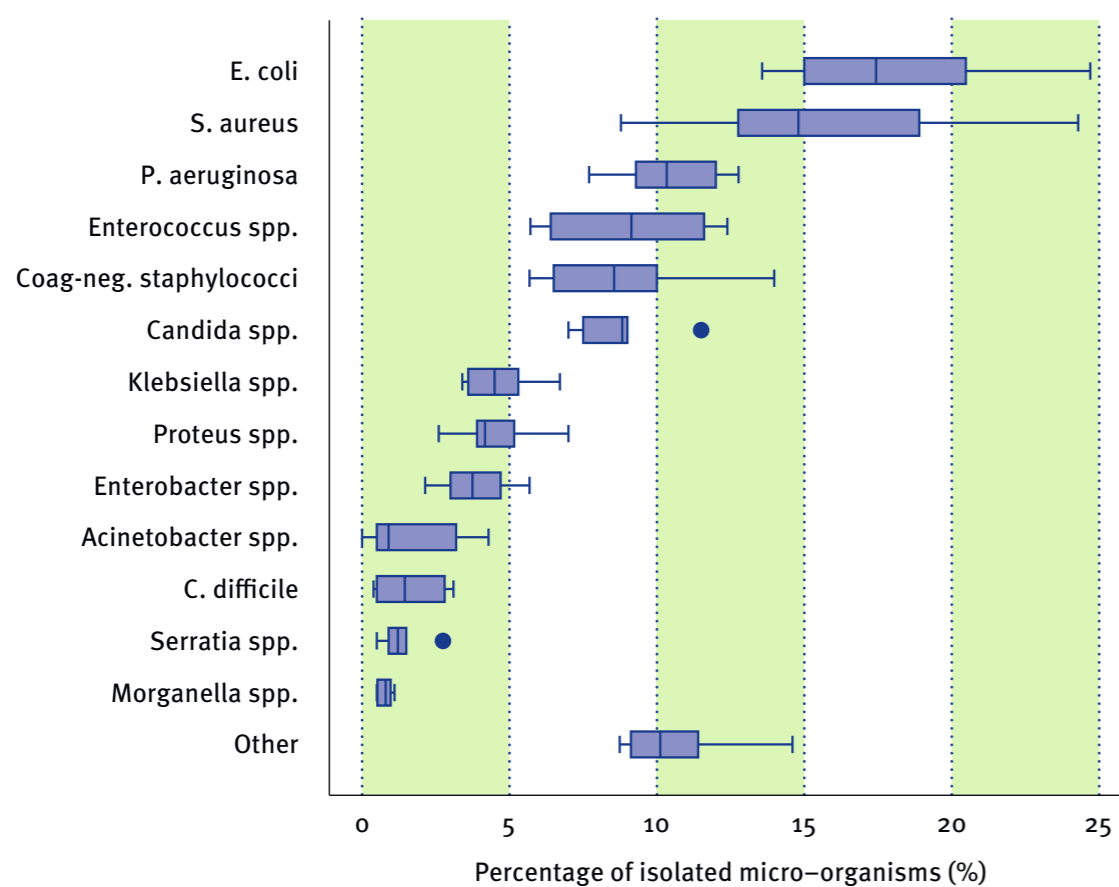
Antimicrobial resistance

Most, although not all, new antibiotic resistance mechanisms were first described in hospital-acquired micro-organisms. Methicillin-resistant *S. aureus*, for example, was a predominantly nosocomial pathogen for a long time until it became increasingly prevalent in other settings such as nursing homes, related to the extensive flow of patients between these two types of institutions and sustained antibiotic selection and cross-transmission in both of them. More recently, other methicillin-resistant *S. aureus* strains have emerged

in the community, such as the community-acquired MRSA strain that carries a gene responsible for the Pantone-Valentine leukocidin toxin, capable of causing invasive infections in healthy subjects⁵⁰; and more recently the multilocus sequence type 398 strain isolated from animals such as pigs and spread to farmers and their families as well as to veterinarians^{51,52,53}. Apart from their resistance to the first line therapy in staphylococcal infections, both of these strains constitute a new challenge to hospital infection control as they represent a new community reservoir that could be imported into the healthcare setting without the risk factors usually recognised in MRSA screening policies. Similarly, extended-spectrum β lactamase (ESBL)-producing *E. coli* is increasingly seen in the community, mostly causing urinary tract infections (but also bloodstream infections and gastro-enteritis) in the community and in nursing homes⁵⁴. ESBL-producing Enterobacteriaceae are resistant to all penicillins and cephalosporins, but are also resistant to other classes of antibiotic, especially fluoroquinolones and co-trimoxazole, leaving only a few other therapeutic options such as carbapenems.

However, resistance to carbapenems has also emerged in nosocomial ESBL-producing Enterobacteriaceae such as *Klebsiella pneumoniae* and non-fermenters (*Pseudomonas aeruginosa* and *Acinetobacter baumannii*), leaving very limited (e.g. colistin) or no treatment options for an increasing number of healthcare-associated infections^{55,56,57}. The following are some of the pathogens

Figure 2.2.1. Relative frequency of micro-organisms isolated in nosocomial infections (all types) in six European national or multicentre prevalence surveys



posing a major threat to healthcare systems, but the list is not exhaustive.

- Vancomycin-resistant *Staphylococcus aureus* (VRSA);
- Vancomycin-resistant enterococci (VRE);
- Carbapenem-resistant Enterobacteriaceae;
- Carbapenem-resistant *Pseudomonas aeruginosa*;
- Carbapenem-resistant *Acinetobacter spp.*;
- ESBL-producing Enterobacteriaceae, including community-onset CTX-M producing *Escherichia coli*.

Surveillance of antimicrobial resistance has been successfully implemented in Europe through the EARSS project (European Antimicrobial Resistance Surveillance System), supported by the European Commission's Directorate-General for Health and Consumer Protection. The project was presented in detail in the *Annual Epidemiological Report on Communicable Diseases in Europe 2005* and results for 2006 are summarised in chapter 3, below. While this network succeeded in following up trends, the early detection of bacteria with unusual resistance patterns remains a challenge for Europe (see section 2.8, below).

2.3 SURVEILLANCE OF NOSOCOMIAL INFECTIONS IN EUROPE

Surveillance of nosocomial infections differs significantly from surveillance of antimicrobial resistance. The latter is largely laboratory-based and uses microbiological case definitions, whereas HCAI surveillance

involves active case-finding by infection control teams and clinicians, uses clinical case definitions sometimes without a microbiological component and requires the collection of additional data to determine the infection source and perform inter-hospital comparisons of HCAI rates.

Following the demonstration of the effectiveness of surveillance in the prevention of nosocomial infections in the US⁵⁸ and the success of the National Nosocomial Infection Surveillance Scheme of the Centres for Disease Control (CDC)⁵⁹, several European countries started to set up national networks for the surveillance of nosocomial infections in the early 1990s.

These surveillance networks are all target-oriented, meaning that they focus on a specific type of healthcare-associated infection and/or on a patient population at higher risk⁶⁰. Their primary goal is to offer a standardised methodology to participating healthcare institutions in order to assess their own infection rates, follow them up in time and compare them with the rates of other institutions as a measure of their own performance.

Because national or regional priorities in terms of infection control may differ, many different surveillance protocols have been developed over the years. The protocols that were most common to Member States in the late nineties, the surveillance of surgical site infections and the surveillance of ICU-acquired infections, have been the target for standardisation at the EU level

within the EU-funded HELICS (Hospitals in Europe Link for Infection Control through Surveillance) project since 2000^{61,62}. Table 2.3.1 shows an overview of the different surveillance protocols that have been implemented in EU Member States (status 2007). Hospital-wide surveillance of all types of infections, though interesting from a public health point of view, is rarely implemented because it does not enable meaningful comparisons of rates between institutions at an acceptable workload for the infection control staff, nurses or clinicians that have to collect the data. Instead, increasing numbers of countries are performing national point prevalence surveys. These make nationwide estimates of the burden of HCAI possible but do not usually provide sufficient precision for individual hospitals to make a reliable interpretation of their own figures. In eastern Member States, nosocomial infections are often still part of the list of mandatory reportable diseases. However, these systems are likely to suffer from under-reporting because most surveillance systems are primarily based on confidential treatment and feedback of hospital infection rates. Moreover, case-based reporting of on average approximately 10 000 nosocomial infections per one million inhabitants and per year (see burden estimates below) in the absence of meaningful denominator data does not serve the local surveillance objectives of the hospital.

Although the table also includes hospital-based surveillance networks of antimicrobial resistance, the well-known lab-based

EARSS surveillance scheme that collects data from over 800 laboratories serving more than 1300 hospitals in 31 countries (including all but one of the EU Member States)⁶³, is not listed here. Unlike EARSS, hospital AMR surveillance networks are mostly run by the hospital infection control staff and look at both percentage resistance and incidence rates of (new) hospital-acquired cases as an indicator of cross-transmission. Data collection in EARSS is mostly done by microbiologists and does not look at hospital-acquired cases. For example, the hospital admission date is often not available in the participating laboratories and therefore it is only available for approximately 40% of known inpatients with invasive isolates reported to EARSS (EARSS, J. Monen, personal communication). On the other hand, EARSS provides more precise and validated data on the percentage resistance in isolates from invasive samples (including imported bloodstream infections from the community or nursing homes), using standardised definitions (breakpoints) for antimicrobial susceptibility data.

The coordination of the surveillance of nosocomial infections is usually performed by the national surveillance institutes or by other institutions (such as universities) that have been designated for that task by the national health authorities or surveillance institutes. In countries with a strong regionalisation of hospital infection control policies, setting up coordinated national initiatives for HCAI surveillance is a difficult process (e.g. Sweden, Italy) and in some cases the initiative for setting up a network

Table 2.3.1. Overview of different surveillance protocols/modules implemented by national or regional networks for the surveillance of healthcare-associated infections in EU countries

	Austria	Belgium	Bulgaria	Croatia	Cyprus	Czech Republic	Denmark	Estonia	Finland	France	Germany	Greece	Hungary	Ireland	Italy	Latvia	Lithuania	Luxembourg	Malta	Netherlands	Norway	Poland	Portugal	Romania	Slovakia	Slovenia	Spain	Sweden	UK-England(f)	UK-Northern Ireland	UK-Scotland	UK-Wales	
Surveillance of surgical site infections (HELICS)	x	x				(b)		x	x	x	(c)	x		(d)	x					x	x	x	x			(e)	x	x ^(a)	x ^(a)	x ^(a)	x ^(a)		
Surveillance of surgical site infections in one-day surgery										x																							
Surveillance of surgical site infections in cardiac surgery																				x													
Surveillance of surgical site infections in neurosurgery																																	
Surveillance of ICU-acquired infections (HELICS)	x	x	x			(g)		x	x	(c)	x	x	x			x	x		(b)	(e)	(f)	x	(g)	(h)		x	(e)		(i)				
Surveillance of central line infections in ICU										(i)																					x		
Surveillance of nosocomial infections in neonatal ICUs											x																						
Surveillance of central catheter colonisation in neonatal ICUs										(i)																							
Surveillance of central line infections in neonatal ICUs										(i)																							
Surveillance of bacteremia	x							x	x																		x				x		
Surveillance of central line infections																				x													
Surveillance of bloodstream infections with S. aureus																	x										x ^(a)						
Surveillance of bloodstream infections with MRSA																	x														x ^(a)		
Surveillance of GRE bloodstream infections																											x ^(a)						
Surveillance of ventilator-associated pneumonia																				x													
Surveillance of urinary tract infections										(i)																						x	
Surveillance of device-associated infections											x																						
Surveillance of C. difficile infections		x ^(b)						x		x																	x ^(b)	x	x	x			
Surveillance of MDR bacteria in hospitals										x																							
Surveillance of MRSA in hospitals		x ^(b)							x	x						x																	
Surveillance of MDR gramnegatives in hospitals		x								x																							
(Repeated) prevalence surveys of HCAI in hospitals	x ^(c)	x ^(c)				x	(g)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Surveillance of nosocomial infections in Onco/BMtransplant											x																						
Surveillance of dialysis-related infections										(i)																							
Surveillance of nosocomial infections in obstetric wards										(i)																							
Surveillance of rotavirus infections in paediatric wards										(i)																							
Surveillance of RSV infections in paediatric wards																																x	

Table 2.3.1 continued

	Austria	Belgium	Bulgaria	Croatia	Cyprus	Czech Republic	Denmark	Estonia	Finland	France	Germany	Greece	Hungary	Ireland	Italy	Latvia	Lithuania	Luxembourg	Malta	Netherlands	Norway	Poland	Portugal	Romania	Slovakia	Slovenia	Spain	Sweden	UK-England(f)	UK-Northern Ireland	UK-Scotland	UK-Wales	
Surveillance of HCAI outbreaks									(h)	x					x ^(h)																x	x	
Surveillance of hand hygiene compliance		x									x																						
Surveillance of hand alcohol use		x								x	x																						
Surveillance of accidental blood exposure in healthcare workers		x								x																							
Surveillance of antibiotic consumption in hospitals		x																															
Repeated point prevalence surveys of antibiotic use							x	x							x												x						

- (a) Mandatory participation;
- (b) Surveillance discontinued;
- (c) Data not transferred to HELICS;
- (d) Pilot network;
- (e) Results not yet available;

- (f) Public disclosure of individual (hospital) rates;
- (g) Prevalence survey(s) in one or few hospitals;
- (h) Food- and waterborne disease outbreaks covered by specific system;
- (i) Modules developed by one or some of the five regional sub-networks (C. Clin) in France.

has been led by the national societies for infection control without formal collaboration with the national institute (e.g. Italy, Poland).

Table 2.3.2 shows an overview of coordinating institutes with their respective websites for a selected number of countries.

2.4 COMPARABILITY OF NOSOCOMIAL INFECTION RATES

Since inter-hospital comparisons are an essential component of surveillance of nosocomial infections, risk adjustment is important for the interpretation of the data and to correct for the case-mix variations between institutions. For example, the

NNIS and HELICS protocols for the surveillance of surgical site infections include risk factors in order to calculate a risk index as developed by the US CDC⁶⁴ which is used to stratify or standardise the surgical site infection rates. This, however, assumes that the surveillance teams in the hospitals collect risk factor data for each patient undergoing one of the surgical procedures in the selected categories. Similarly, adjustment for intrinsic and extrinsic risk factors in the ICU requires data collection at patient level.

Differences between case definitions and surveillance methodologies create further variations in nosocomial infection rates (as for all types of surveillance). This issue is particularly apparent when it comes to

Country	Network acronym	Website	Coordination
Austria	ANISS	www.meduniwien.ac.at/hygiene/?c=aniss&s=krankenh aushygiene	Austrian Nosocomial Infection Surveillance System, Medical University of Vienna
Belgium	NSIH	www.iph.fgov.be/nsih	National Surveillance of Healthcare-associated infections and antimicrobial resistance, Scientific Institute of Public Health (IPH), Brussels
Croatia			Reference Centre for Hospital Infections, Zagreb
Finland	SIRO	www.ktl.fi/siro	Finnish Hospital Infection Programme (SIRO), National Public Health Institute (KTL), Helsinki
France	RAISIN	www.invs.sante.fr/raisin	Réseau d'Alerte, d'Investigation et de Surveillance des Infections Nosocomiales (RAISIN), under the auspices of the Institut de Veille Sanitaire (InVS)
FR-East	C.CLIN Est	www.cclin-est.org	
FR-Paris-Nord	C.CLIN Paris-Nord	www.cclinparis-nord.org	
FR-South-east	C.CLIN Sud-Est	cclin-sudest.chu-lyon.fr	
FR-South-west	C.CLIN Sud-Ouest	www.cclin-sudouest.com	
FR-West	C.CLIN Ouest	www.cclinouest.com	
Germany	KISS	www.nrz-hygiene.de/surveillance/surveillance.htm	German Nosocomial Infection Surveillance System (KISS), National Reference Centre for Nosocomial Infection Surveillance, Charité Medical University, Berlin
Hungary		www.oek.hu/oek.web*	Johan Béla National Centre for Epidemiology, Budapest
Italy	SPIN-UTI		Regional Health Authority of Emilia-Romagna, Bologna; ICU network: Gruppo Italiano Studio Igiene Ospedaliera (GISIO)
Lithuania		www.hi.lt => Hospitalinės infekcijos	Institute of Hygiene, Vilnius
Luxembourg	NOSIX	www.crp-sante.lu*	Centre de Recherche Public de la Santé, Luxembourg
Netherlands	PREZIES	www.prezies.nl	Prevention of Nosocomial Infection through Surveillance (PREZIES), National Institute for Public Health and Environment (RIVM) and the Dutch Institute for Healthcare Improvement (CBO)
Norway	NOIS	www.fhi.no => NOIS	Norwegian Institute of Public Health (FHI), Oslo
Poland			Polish Society of Hospital Infections; National Institute of Public Health, Warsaw

Country	Network acronym	Website	Coordination
Spain	ENVIN (ICU), EPINE (prevalence)	www.mpsp.org/mpsp/epine; www.iscii.es*	Envin: Hospital Val d'Hebron, Barcelona; SSI surveillance by Carlos III Institute of Health, Madrid
UK-England	SSISS (SSI)	www.hpa.org.uk/infections/topics_az/hai/default.htm	Health Protection Agency (HPA), London
UK-Northern Ireland	HISC	www.hisc.n-i.nhs.uk	Northern Ireland Healthcare-associated Infection Surveillance Centre (HISC), Belfast
UK-Scotland	SSHAIP	www.hps.scot.nhs.uk/haic/sshaip/index.aspx	The Scottish Surveillance of Healthcare Associated Infection Programme (SSHAIP), Health Protection Scotland, Glasgow
UK-Wales	WHAIP	www.wales.nhs.uk/sites3/home.cfm?orgid=379	Welsh Healthcare Associated Infection Programme (WHAIP), National Public Health Service (NHS) Wales

* websites without specific pages for HCAI surveillance.

inter-country or inter-network (within the same country) comparisons. Examples of issues where crucial differences arise include: whether the same patients are included in the denominator; whether only the first or all infection episodes are counted; whether exposure is counted as up until the first infection or for the entire stay (e.g. in the ICU, mechanical ventilation given after onset of a ventilator-associated pneumonia is likely to be treatment of a worsening respiratory condition)^{65,61}. Since case definitions and surveillance methods are mostly agreed on within the national or regional network of hospitals, changing those to EU-agreed definitions and methods as pursued by the HELICS network, was a long-term process. Indeed, some national networks are still using definitions and methods that are not fully compatible with the European definitions. Alongside the HELICS standardisation process, a par-

allel process has been running at the national level to reach a consensus between regional networks on methods and definitions (mainly in France, but to some extent also in the UK).

Finally, data validity is of course a major issue in the surveillance of HCAI, and field validity studies performed by some surveillance networks have clearly shown that the sensitivity of NI surveillance is far from optimal⁶⁶. Even within the same network with the same case definitions, hospitals' interpretations of those definitions may still differ. There can also be differences between the case finding processes in each hospital and different attitudes towards reporting nosocomial infections to a coordinating centre that is often associated with the health authority; there can be a reluctance to report, even when individual hospital data are treated confidentially and only reported

to the participating institution. Indeed, the easiest way to officially have zero infections is not to report any, and that has essentially been the major argument against public disclosure (or disclosure to health authorities by the surveillance coordinating centre) of nosocomial infection rates that include the identity of the hospital.

In order to further assess and improve the comparability and quality of the data collected in HCAI surveillance networks, a European validation study based on a standardised validation methodology should be carried out. Such a study would enable an assessment of the sensitivity of the different surveillance networks and an exploration of the real differences between case definitions judged against the same golden standard.

2.5 BURDEN OF NOSOCOMIAL INFECTIONS

Hospital-wide incidence figures for all types of nosocomial infections are not available from European countries. The type of surveillance that generates such data was abandoned worldwide in the early nineties because of poor cost-effectiveness in terms of prevention of nosocomial infections⁶⁰. Given this lack of hospital-wide figures, the total annual number of nosocomial infections occurring in the EU has been estimated based on data from recent national or multicentre prevalence surveys (see Section 2.2). It should, however, be stressed that these estimates must be interpreted and

used with caution since they are based on the following assumptions.

Firstly, the prevalence surveys underlying the estimates use different methods (inclusion criteria, case definitions, case finding methods, etc.), hence figures for individual countries can not be compared. However, we do assume that the average of these figures also represents an average methodology which would apply to the entire EU.

Secondly, we assume that the average percentage prevalence from data of different recent years would not be significantly different from the average today.

Thirdly, the method of converting prevalence to incidence is itself based on several assumptions such as the average length of hospital stay for infected and non-infected patients.

Fourthly, estimating mortality attributable to HCAI is probably one of the most discussed areas in epidemiology due to the underlying illness of hospitalised patients. Since no gold standard exists, an often cited reference from scientific literature was used^{38,67}. Using another reference or methodology such as chart reviews⁶⁸ or use of national registries and 28-day mortality⁶⁹ would result in different attributable mortality estimates.

Finally, for the calculation of burden estimates we used the average unit cost per patient-day from cardiovascular units available from the only reference to our knowledge

providing EU-wide inpatient day costs⁷⁰. These data may differ from the cost per bed day for patients with healthcare-associated infections in general.

Taking into account these important limitations, the total annual number of HCAI in hospitals can be estimated by converting the mean prevalence of 7.1% (see Table 2.2.1) to a cumulative incidence figure of approximately 5.1% according to the method described by Gastmeier et al.⁷¹. This figure compares relatively well with the best nationwide figure of 5.7 per 100 admissions so far available from the US⁷². According to Eurostat figures for the EU 27 (2005 figures completed by earlier years if missing, ref. <http://epp.eurostat.ec.europa.eu/> and Health in Europe 2005 pocketbook edition), the number of hospital admissions in the EU 27 (498 million inhabitants) is approximately 81 million per year (on average 16 247 admissions per 100 000 inhabitants per year). The yearly number of patients with at least one nosocomial infection in the EU 27 can thus be estimated at 4 131 000 patients. Since patients will often get more than one infection during the same hospitalisation (average from the national prevalence surveys review is 1.1 infections per infected patient) the yearly number of nosocomial infections can be estimated at 4 544 100.

The impact of nosocomial infections on the length of stay in the hospital and mortality (attributable morbidity and mortality) depends on the type of infection (highest for pneumonia and bloodstream infections) and estimates vary considerably in scien-

tific literature. Based on overall estimates of attributable mortality of nosocomial infections by the US CDC^{38,67}, approximately 37 000 deaths (0.9%) caused directly by nosocomial infections occur every year in the EU 27 and infections contributed to an additional 111 000 deaths. Nosocomial infections also generate approximately 16 million extra days of hospital stay per year (an average of four days per infection³⁸), at a considerable cost and creating a significant burden for healthcare systems in Member States.

Assuming an average hospital cost of EUR 435 per day⁷⁰, the total annual healthcare cost of nosocomial infections for the EU 27 can be estimated at EUR 7 billion per year, not considering any indirect costs linked to loss of income as the result of illness and death, nor the intangible costs associated with the physical and emotional pain and suffering.

2.6 PREVENTABILITY OF NOSOCOMIAL INFECTIONS

Many nosocomial infections are not avoidable in real-life hospital conditions, because of the underlying illness of the hospitalised patient (e.g. impaired immunity), the invasive procedures to which patients sometimes have to be exposed in order to survive (e.g. mechanical ventilation of a comatose patient over several weeks in the ICU), and the potential pathogens that all humans carry (endogenous flora) and that may cause severe infections if normal host defence mechanisms are breached. The question is

what represents the irreducible minimum, for endemic nosocomial infections as such, but also for the cross-transmission of resistant or more virulent nosocomial pathogens (potentially causing exogenous nosocomial infections) and for the selection of multi-resistant micro-organisms by antibiotic use. Estimates of the preventable proportion of nosocomial infections have for a long time been based on the results of the landmark SENIC study⁵⁸ showing that with intensive infection control and surveillance programmes an overall reduction of 32% in nosocomial infection rates could be obtained in a five-year period. A more recent review of 30 multi-modal intervention studies and studies assessing exogenous cross-infection, found a minimum reduction effect of 10% to a maximum effect of 70%, depending on the setting, study design, baseline infection rates and type of infection⁷³. The authors concluded that on average 20–30% of all nosocomial infections occurring under current healthcare conditions can be prevented. An even larger proportion (>50%) of device-associated bloodstream infections seems to be avoidable, with studies investigating multi-modal interventions reporting reductions in catheter-related bloodstream infections ranging from 29% to 95%^{74,75}. As for ventilator-associated pneumonia, studies suggest that average reductions of more than 40% are possible⁷⁶.

2.7 PREVENTION AND CONTROL MEASURES

HCAI prevention and control is essentially based on: prevention of cross-transmission

of nosocomial pathogens; prevention of bacteria causing infections when normal barriers are breached; and prevention of the selection of resistant pathogens by inappropriate antibiotic use.

Healthcare-associated infection control measures are usually subdivided into standard measures, to be applied by the healthcare workers in all circumstances (e.g. hand hygiene), and additional precautions, to be taken when dealing with patients that are colonised or infected with particular micro-organisms. These precautions may vary according to the pathogen involved (essentially isolation measures).

Numerous guidelines on prevention of healthcare-associated infections have been developed, both by the US Centers for Disease Control and Prevention, and by other national or regional bodies in European and other countries (e.g. by specifically designated national expert committees, public health institutes or scientific associations). Table 2.7.1 gives an overview of the most common guidelines developed at the national level.

Hand hygiene has been recognised as the most important standard measure to prevent cross-transmission of nosocomial micro-organisms and has regained considerable attention in recent years. Since any patient or healthcare worker is potentially colonised with important nosocomial pathogens, even after negative screening tests at admission or at some stage during the stay in the institution, hand hygiene has to be applied rigorously before and after contact with any patient.

Table 2.7.1. Frequently developed guidelines and recommendations for the prevention of healthcare-associated infections

General guidelines:
Prevention of healthcare-associated infections
Standard precautions
Hand hygiene
Isolation precautions
Infection site-specific guidelines:
Prevention of intravascular device-related infections
Prevention of surgical site infections
Prevention of catheter-associated urinary tract infections
Prevention of healthcare-associated pneumonia
Pathogen (antimicrobial resistant and other)-specific guidelines:
General guidelines for multidrug-resistant organisms
Prevention and control of MRSA in hospitals and/or nursing homes
Prevention and control of ESBL-producing bacteria
Prevention and control of <i>C. difficile</i> infections
Examples of guideline websites (accessed July 2008):
US CDC: http://www.cdc.gov/ncidod/dhqp/guidelines.html
France: http://nosobase.chu-lyon.fr/recommandations/recommandations.htm
United Kingdom: www.hpa.org.uk : Home → Infectious Diseases → Infections A–Z → Healthcare Associated Infections → Guidelines
Germany: www.rki.de : Startseite → Infektionsschutz → Krankenhaushygiene → Empfehlungen der Kommission für Krankenhaushygiene
The Netherlands: www.wip.nl
Belgium: www.health.fgov.be/CSS_HGR
Ireland: http://www.ndsc.ie/hpsc/Publications
Lithuania: www.ulpkc.lt/ulpkc.metodines.php (nr 1.7-202)

Recommendations for the prevention of specific infection types mainly concern healthcare-associated and ventilator-associated pneumonia, catheter-related bloodstream infections and urinary tract infections. In particular, for the prevention of hospital-acquired pneumonia (HAP), the most common healthcare-associated infec-

tion contributing to death, many specific recommendations are still controversial, resulting in important variations between different guidelines. Some authors therefore propose the development of comprehensive pan-European HAP guidelines that could rationalise the conflicting proposals, provide a useful resource and limit guideline pro-

Table 2.7.2. European Task Force (ETF), Centers for Disease Control and Prevention (CDC), Canadian Critical Care Society (CCCS) and American Thoracic Society and Infectious Diseases Society of America (ATS-IDSA) recommendations regarding non-pharmacological and pharmacological measures to prevent ventilator-associated pneumonia. Adapted from Lorente et al.⁷⁸

	ETF ⁷⁹	CDC ⁸⁰	CCCS ⁸¹	ATS-IDSA ⁸²
Publication year	2001	2004	2004	2005
Non-pharmacological measures				
<i>Oral intubation better than nasal</i>	NC	IB	REC	II
<i>Optimal pressure of endotracheal tube cuff</i>	NC	NR	NR	II
Subglottic secretion drainage	SC	II	Cons	I
Early extubation	NR	IB	NR	II
<i>Avoid re-intubation</i>	NC	II	NR	I
Non-invasive ventilation	SC	II	NR	I
Tracheostomy: early better than late	NR	NR	Insuf	NR
Respiratory filters	NR	U	NR	NR
<i>Routine change of ventilator circuits</i>	NO: NC	NO: IA in heat and moisture exchanger/ II in heated humidifier	NO	NO
Heat and moisture exchanger better than heated humidifier	SC	U	REC	I: is the same
Tracheal suctioning system: closed better than open	SC	U	NR	NR
Routine change of closed tracheal suctioning system	SC	U	NO	NR
Sterilisation or disinfection of respiratory devices	NR	IB	NR	NR
Barrier measures	NC	IA	NR	I
Kinetic or standard beds	NR	U	Cons	NR
<i>Semirecumbent position (30–45°)</i>	NC	II	REC	I
Feeding: post-pyloric better than gastric	SC	U	NR	NR
Pharmacological measures				
Selective digestive decontamination	NC in some patients	U	Insuf	I
Preventive intravenous antibiotics	SC	U	Insuf	I at time of intubation
Chlorhexidine oral rinse	NR	II in cardiac surgery	NR	I in cardiac surgery
Sucralfate better than ranitidine	SC	U	Insuf	I: is the same
<i>Avoidance of deep sedation and paralytic agents</i>	NC	NR	NR	II

Cons: Considered;

I: The evidence is from well-conducted, randomised controlled trials;

IA: The evidence comes from well-designed experimental, clinical or epidemiological studies;

IB: The evidence comes from certain clinical or epidemiological studies;

II: The evidence comes from well-designed, controlled trials without randomisation;

Insuf: Insufficient evidence;

NC: Not controversial;

NO: No, not recommended, the recommendation is of no use;

NR: The guideline did not review this issue;

REC: Recommended;

SC: Still controversial;

U: Unresolved.

liferation⁷⁷. Measures to prevent ventilator-associated pneumonia have recently been reviewed by Lorente et al.⁷⁸ and are shown in Table 2.7.2. Non-controversial recommendations are shown in italic.

Recently, several countries also developed specific recommendations for the prevention of *C. difficile* infection (CDI)^{83,84,85,86}. In 2006, ECDC created a working group on *C. difficile* in order to estimate the spread and burden of the ribotype 027 epidemic in Europe and coordinate actions for risk assessment. It developed a common background paper including a European case definition for CDI⁸⁷ and reviewed CDI control measures as guidance for the elaboration of national CDI guidelines⁸⁸.

2.8 CURRENT CHALLENGES

The challenges in the field of HCAI surveillance, prevention and control are important and diverse^{89,90}. In the European context, priorities can be identified at different levels, and some of the challenges for the next decade are discussed below.

Surveillance of healthcare-associated infections

A major issue for the near future is the further extension of the European surveillance of healthcare-associated infections to all EU Member States. The existing European protocols for the surveillance of surgical site infections and the surveillance of ICU-acquired infections that were developed by HELICS have already achieved a high degree

of methodological harmonisation between countries and have been implemented in a (small) majority of Member States (Table 2.3.1, above). Therefore, although some methodological compatibility issues still remain to be resolved in a limited number of countries, these constitute the most logical choice for further extension of surveillance in Europe integrated in ECDC surveillance activities.

In addition, the question should be raised as to whether traditional surveillance methods form the best basis for a sustainable and cost-effective European surveillance system in the long term. With hospital information systems becoming gradually more sophisticated throughout Europe, an increasing amount of data is made available for electronic data collection on infections and risk factors⁹¹, thus creating many opportunities to improve the efficiency of the work of the hospital infection control staff for surveillance as well as for case management (e.g. follow-up of isolation procedures).

Moreover, in order to respond to the data needs of regional, national and international public health authorities, hospital-wide data on healthcare-associated infections should be collected in a cost-effective way, e.g. by the organisation of an EU-wide prevalence survey based on a commonly agreed protocol. Many countries have now implemented such national one-day point prevalence surveys of nosocomial infections, often on a regular basis (as an alternative method to hospital-wide surveillance) and mostly in acute care settings (Section 2.2).

The methods used, however, differ between countries and need further standardisation at the EU level.

Finally, the extension or establishment of other surveillance components at the EU level should be considered. For instance, prospective surveillance of the incidence and severity of *C. difficile* infection (CDI) would allow for early detection of any increasing incidence in Member States where epidemics with the more virulent strain PCR ribotype 027 (and possibly other ribotypes) have not yet emerged. Similarly, surveillance systems should be capable of capturing clusters of other emerging pathogens or unusual variants of old pathogens such as PVL-positive CA-MRSA or the animal MRSA strain MLST type ST398^{92,93}. Such surveillance systems would mostly have to rely on molecular typing data and therefore would require a clear strategy from ECDC in order to facilitate standardisation of molecular typing where possible and promote or support the use of international internet-based typing databases, both for surveillance and for infection control purposes^{94,95,96,97,98,99}.

Support to national programmes for infection control in healthcare facilities

The creation and coordination of national and regional infection control programmes, including those for surveillance, depend on the priority that national or regional decision makers have given to HCAI prevention and control. This governs the resource allocation and policy setting (legislation, recommendations, etc.) at the level of public health administration, national coordinating

bodies for HCAI and/or AMR, surveillance institutes (dedicated epidemiologists) and hospitals (infection control staff, data nurses, etc.). The effects of such decisions can be seen in diverse ways: several EU Member States face a lack of financial or human resources to develop and support such programmes, while in other EU Member States the development of a coherent approach has been hampered by the regionalisation of hospital policy competencies.

Hence, there is a need for European recommendations on HCAI prevention and control in order to ensure that Member States' infection control capacities meet common minimal standards, thus improving patient safety across European health services. The European Commission has worked on a first version of such recommendations and has published them for public consultation¹⁰⁰. The implementation of these common standards could then be supported by the EU, by, for example, ECDC country visits and the provision of training courses for policymakers and surveillance network coordinators as well as for hospital intensive care staff. Surveillance of a limited list of infection control structure and process indicators at the hospital and national levels should be carried out by ECDC to monitor the implementation of the recommendations.

Increasing patient mobility, the Global Patient Safety Challenge and Hand Hygiene

The extent of mobility in Europe has changed considerably in recent years. Healthcare systems are increasingly chal-

lenged to provide optimal access to and quality of healthcare to citizens of other Member States. Rosenmöller et al. distinguished five categories of mobile patients: citizens on holiday requiring healthcare; citizens who retire to a different country or work abroad and require healthcare; people sharing close cultural or linguistic links with the region where care is provided (e.g. treatment close to home that happens to be cross-border); people seeking healthcare cross-border because of perceived advantages (e.g. shorter waiting lists, cheaper treatments, better quality); and patients sent abroad by their own health system to overcome capacity restrictions at home¹⁰¹. These increasingly complex cross-border healthcare contacts present a challenge to EU politicians to ensure access to affordable quality care at least at the same level as that provided in the home country, as illustrated by the recently published proposal for an EU directive on cross-border healthcare (2 July 2008, www.eurofedop.org). They also demand that the European health services, including the infection control community, raise their standards to the highest possible level to ensure patient safety.

This evolving dimension of patient mobility has also contributed to the renewed interest in patient safety worldwide. In October 2004, WHO launched the World Alliance for Patient Safety (www.who.int/patientsafety) in response to a World Health Assembly Resolution (2002) urging WHO and its member states to pay the closest possible attention to the problem of patient safety. The first programme launched by the Global

Patient Safety initiative in 2005, Clean Care is Safer Care, focuses on hand hygiene¹⁰², the cornerstone of infection prevention.

Even before bacteria were discovered, Ignace Semmelweis showed the dramatic impact of hand hygiene on post-partum mortality. In the late 1990s, D Pittet et al showed the effect of repetitive hand hygiene campaigns on the reduction of nosocomial infection rates and resistance rates in a modern university hospital¹⁰³. It became clear that compliance of healthcare staff with hand hygiene recommendations is not higher than 50% on average in baseline conditions¹⁰⁴. Several EU Member States started implementing national campaigns, with increases in mean compliance rates of approximately 50% before the campaign to 70% after the campaign and subsequent decrease in national MRSA incidence rates in Belgium¹⁰⁵.

These experiences show that there is room for dramatic improvement of compliance with the most basic but also the most effective infection control measure, even in countries that have a long history of national and funded infection prevention, control and surveillance programmes and with infection control staff in place. ECDC can support Member States in raising the standard of hand hygiene in healthcare institutions by providing standardised tools and technical assistance for Member States implementing the principles of the WHO Clean Care is Safer Care campaign, thus also pursuing all EU countries' adherence to the First Global Patient Safety Challenge (www.who.int/gpsc).

Early detection of unusual resistant pathogens and outbreaks of HCAI

A second consequence of the increasing mobility of patients is the international transmission of nosocomial pathogens that may potentially spread in other Member States. Examples of this are the transmission of pathogens between French hospitals and Belgian nursing homes of VEB1-producing *Acinetobacter baumannii*^{106,107}, the likely transmission of *C. difficile* ribotype 027 strains from Belgian nursing homes to French hospitals¹⁰⁸, a cluster of multidrug-resistant *K. pneumoniae* in France with an index case transferred from Greece for a liver transplant¹⁰⁹ or the transatlantic spread of the USA300 clone of CA-MRSA in a Swiss health worker on a clinical fellowship in the US¹¹⁰. Timely reporting of information on selected unusual multidrug-resistant bacteria and nosocomial epidemics of public health importance should be promoted at the level of Member States' laboratories and hospitals. Relevant information should be shared at the European level using existing systems such as the Early Warning and Response System, epidemiological bulletins such as *Eurosurveillance*, or specific collaborative information systems on AMR and HCAI integrated in the epidemiological information system of ECDC. In parallel, the capacity to respond to these threats at the institutional, national and European level should be enhanced.

Surveillance and infection control in nursing homes

Healthcare-associated infections and infection control represent major and rapidly in-

creasing challenges for European long-term care facilities (LTCF) and nursing homes. The higher speed with which the burden of this problem is increasing in these settings as compared with acute care hospitals is attributable to a variety of factors. Not least of these is that the European population is ageing rapidly. The over 65s represented 15% of the population in 1997, 17% in 2007¹¹¹ and are forecast to represent 29.4% of the general population in 2050¹¹². At the same time, healthcare systems are striving for cost optimisation which results, amongst other things, in shorter hospital stays and early discharge. These two factors combined have led to a rapid rise in the demand for nursing homes and other social and healthcare services for the elderly such as long-term care facilities, residential homes for the elderly and home care.

Further, the fact that the frail elderly more frequently require hospital care has led to an extensive exchange of nosocomial pathogens between hospitals and nursing homes, resulting in steadily growing numbers of nursing home residents colonised with formerly typical 'hospital bugs' such as MRSA^{113,114} or ESBL-producing Enterobacteriaceae. Unfortunately, most European countries have invested far fewer resources for infection control in nursing homes than in hospitals, which in combination with a frequent lack of rational antibiotic policy, has contributed to the spread of these pathogens within the nursing homes, thereby maintaining a reservoir that threatens infection control in the hospitals. Because of age-related dysfunctions of the

immune system and physiological changes, the elderly are more sensitive to infection and therefore predisposed to the most frequent infections occurring in nursing homes: urinary tract infections, pneumonia, skin and soft tissue and gastro-intestinal infections (in particular those associated with antibiotic use, such as *C. difficile* infection)¹¹⁵. Compounding the problem, these infections in colonised nursing home residents are more likely to be caused by multidrug-resistant pathogens that increase morbidity, mortality and costs, as shown by various studies^{116,117,118,119,120}.

Despite the evidence, national or multicentre data on healthcare-associated infections in nursing homes or long-term care facilities are very scarce and surveillance or repeated prevalence surveys are only carried out in Norway. Therefore, it is also very difficult to estimate the size of the problem of HCAI in nursing homes and to follow up any impact of infection control interventions. Moreover, unlike the US, where 1.6 million certified nursing facility beds (5.5 beds per 1000 population) were registered in 2006 compared to 2.7 hospital beds per 1000 population¹²¹, Europe has no reliable data on the number of nursing home beds, partly because the term 'nursing home' is poorly defined and encompasses different types of structures. For instance, the number of nursing home beds is higher than the number of hospital beds in several EU countries (e.g. approximately twice as high in Belgium and 1.5 times higher in England¹²²), but may be much lower in countries where the involvement of the public sector in long-term care

is limited¹²³. HCAI prevalence data from one region in Italy⁶ and nationwide figures from Norway^{29,124} where the prevalence of healthcare-associated infections in long-term care facilities was 8.4% and 7.2% (mean from last three prevalence surveys in Norway) respectively, suggest that the size of the problem of HCAI in terms of absolute numbers may be at least as important as in acute care hospitals, with rapidly increasing problems of antimicrobial resistance and limited infection control infrastructure in most countries. The surveillance, prevention and control of healthcare-associated infections and antimicrobial resistance at the institutional, regional or national and European level is therefore one of the main challenges of the next decade. The creation of an EU-wide network for the surveillance of HCAI and infection control process and structure indicators tailored to the nursing home setting should be one of the first steps. Preparatory work toward this has been undertaken in recent years by the IPSE project (www.ecdc.europa.eu/IPSE). Such a network could be developed in collaboration with the nursing home sub-project on antimicrobial use from ESAC (www.esac.ua.ac.be).

References

1. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988 [published erratum appears in Am J Infect Control 1988 Aug;16(4):177]. Am J Infect Control. 1988;16:128-140.
2. Horan,TC and Emori, TG Definitions of key terms used in the NNIS System. Am J Infect Control 1997;25:112-116.
3. Friedman, ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002; 137:791-797.
4. Mylotte JM. Nursing home-acquired pneumonia. Clin Infect Dis. 2002 Nov 15;35(10):1205-11. Epub 2002 Oct 28.
5. Mylotte JM. Nursing home-acquired bloodstream infection. Infect Control Hosp Epidemiol. 2005;26:833-837.

6. Moro ML, Mongardi M, Marchi M, Taroni F. Prevalence of long-term care acquired infections in nursing and residential homes in the Emilia-Romagna Region. *Infection*. 2007;35:250-255.
7. European Commission Directorate General for Health and Consumer Protection. http://ec.europa.eu/health/ph_information/dissemination/hsis/hsis_11_en.htm
8. Emmerson AM, Enstone JE, Griffin M, Kelsey MC, Smyth ET. The Second National Prevalence Survey of infection in hospitals – overview of the results. *J Hosp Infect*. 1996;32:175-190.
9. Plowman R, Graves N, Griffin MA, Roberts JA, Swan AV, Cookson B, et al. The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. *J Hosp Infect*. 2001;47:198-209.
10. Gastmeier P, Kampf G, Wischniewski N, Hauer T, Schulgen G, Schumacher M, et al. Prevalence of nosocomial infections in representative German hospitals. *J Hosp Infect*. 1998;38:37-49.
11. Réseau d'alerte, d'investigations et de surveillance des infections nosocomiales (RAISIN). Enquête de prévalence nationale 2001 – Résultats. 2001 Available from: http://www.invs.sante.fr/publications/2003/raisin_enp_2001/
12. Prevalence of nosocomial infections in France: results of the nationwide survey in 1996. The French Prevalence Survey Study Group. *J Hosp Infect*. 2000;46:186-193.
13. Sax H, Ruef C, Pittet D. Résultats de l'enquête nationale de prévalence des infections nosocomiales de 2003 (snip03). *Swiss-Noso* 2004;11:1-5. Available from: <http://www.chuv.ch/swiss-noso/>
14. Sax H, Pittet D. Surveillance des infections nosocomiales en Suisse: méthodologie et résultats des enquêtes de prévalence 1999 et 2002. *Swiss-Noso* 2003;10:1-5. Available from: <http://www.chuv.ch/swiss-noso/>
15. Gikas A, Padiaditis J, Papadakis JA, Starakis J, Levidiotou S, Nikolaides P, et al. Prevalence study of hospital-acquired infections in 14 Greek hospitals: planning from the local to the national surveillance level. *J Hosp Infect*. 2002;50:269-275.
16. Lizioli A, Privitera G, Alliata E, Antonietta Banfi EM, Boselli L, Panceri ML, et al. Prevalence of nosocomial infections in Italy: result from the Lombardy survey in 2000. *J Hosp Infect*. 2003;54:141-148.
17. Klavs I, Bufon LT, Skerl M, Grgic-Vitek M, Lejko ZT, Dolinsek M, et al. Prevalence of and risk factors for hospital-acquired infections in Slovenia – results of the first national survey, 2001. *J Hosp Infect*. 2003;54:149-157.
18. Gravel D, Taylor G, Ofner M, Johnston L, Loeb M, Roth VR, et al. Point prevalence survey for healthcare-associated infections within Canadian adult acute-care hospitals. *J Hosp Infect*. 2007;66:243-248.
19. Nicastrì E, Petrosillo N, Martini L, Larosa M, Gesu GP, Ippolito G, et al. Prevalence of nosocomial infections in 15 Italian hospitals: first point prevalence study for the INF-NOS project. *Infection* 2003;31 Suppl 2:10-15.
20. Costa C, Silva G, Rodrigues A, Programa Nacional de Controlo de Infecção. Estudo nacional de prevalência de infecção nosocomial 2003. Instituto Nacional de Saude Dr. Ricardo Jorge. Report N 20051-21.
21. Jensen ET. Prævalensundersøgelsen 2003. CAS-Nyt 2004 Available from: <http://www.ssi.dk/graphics/dk/nyheder/casnyt/2004/pdf/Casnyt100medtoptekst.pdf>
22. Pujate E, Vigante D, Vingre I, Kockina E, Pavlovska D, Mironovska A. Prevalence study of antimicrobial use and hospital infections in Latvia, 2003. *EpiNorth*. 2005;6:35-39. Available from: <http://www.epinorth.org/>
23. Lyytikäinen O, Kanerva M, Agthe N, Mottonen T, Ruutu P, The Finnish Prevalence Survey Study Group. Healthcare-associated infections in Finnish acute care hospitals: a national prevalence survey, 2005. *J Hosp Infect*. 2008 Jul;69(3):288-294.
24. Erntell M, Skoog G, Cars O, Elowson S, Hanberger H, Jorup C, et al. Changes in patterns of antimicrobial use in Swedish hospitals from 2003 to 2006 following the introduction of large-scale nationwide point prevalence studies. 0404. *Clin Microbiol Infect*. 2008; 18th ECCMID/26th ICC. Oral presentations;S88. Available from: http://www.blackwellpublishing.com/eccmid18/PDFs/oral_presentation.pdf
25. Smyth ET, McIlvenny G, Enstone JE, Emmerson AM, Humphreys H, Fitzpatrick F, et al. Four Country Healthcare Associated Infection Prevalence Survey 2006: overview of the results. *J Hosp Infect*. 2008 Jul;69(3):230-248.
26. Réseau d'alerte, d'investigations et de surveillance des infections nosocomiales (RAISIN). Enquête nationale de prévalence des infections nosocomiales, juin 2006. Résultats préliminaires, janvier 2007. Available from: http://www.invs.sante.fr/publications/2007/enp2006_resultats_preliminaires/enp_2006_resultats_preliminaires.pdf
27. Thiolet JM, Lacavé L, Jarno P, Tronel H, Gautier C, L'Heriteau F, et al. Prevalence of nosocomial infections, France, 2006. *Clin Microbiol Infect*. 2008;18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 19–22 April 2008;S25. Available from: http://www.blackwellpublishing.com/eccmid18/PDFs/oral_presentation.pdf
28. Bruun T, and Loewer HL. Prevalence surveillance system of nosocomial infections in Norway. 2007 Aug 30;12(8):E070830.2.
29. Folkehelseinstituttet (Norwegian Institute of Public Health) Surveillance of Communicable Diseases and Nosocomial Infections in Norway 2006. Trends and main prevention strategies. 200745-49. Available from: <http://www.fhi.no/dav/3d326fd31e.pdf>
30. Eriksen HM, Iversen BG, Aavitsland P. Prevalence of nosocomial infections in hospitals in Norway, 2002 and 2003. *J Hosp Infect*. 2005;60:40-45.
31. Reilly J, Stewart S, Allardice GA, Noone A, Robertson C, Walker A, et al. NHS Scotland National HAI Prevalence Survey. Results from the Scottish National HAI Prevalence Survey. *J Hosp Infect*. 2008 May;69(1):62-8.
32. Vaque J, Rossello J, Trilla A, Monge V, Garcia-Caballero J, Arribas JL, et al. Nosocomial infections in Spain: results of five nationwide serial prevalence surveys (EPINE Project, 1990 to 1994). *Nosocomial Infections Prevalence Study in Spain*. *Infect Control Hosp Epidemiol*. 1996;17:293-297.
33. Vaque J, Rossello J, Grupo de Trabajo EPINE Evolución de la Prevalencia de las infecciones nosocomiales en los hospitales Españoles, Proyecto EPINE 10 años, 1990–1999. 1999 Available from: <http://www.mpsp.org/mpsp/epine/>
34. Vaque J, Rodrigo JA, Grupo de Trabajo EPINE Prevalencia de las infecciones en los hospitales españoles. Estudio EPINE. Resultados de los estudios de 2004, 2005, 2006 y 2007, y evolución 1990–2007. *Medicina Preventiva* 2008;14:5-71.
35. Valinteliene R, Jurkuvenas V. Prevalence of nosocomial infections in Lithuania. *Clin Microbiol Infect*. 2008;18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 19–22 April 2008 ;S209-P806. Available from: http://www.blackwellpublishing.com/eccmid18/PDFs/poster_presentation.pdf
36. Higienos Institutas, Hospitalinių infekcijų priežiūros ir kontrolės programa. Infekcijų ir jų rizikos veiksnių paplitimo tyrimo lietuvis ligoninėse ataskaita. Available from: http://www.hi.lt/images/hosp_inf/atask/2007_papl_ataskaita.pdf
37. PREZIES PREZIES landelijk surveillance netwerk ziekenhuisinfecties. Resultaten prevalentiestudie maart 2007. 2007 Available from: <http://www.prezies.nl/prev/index.html>
38. Emori TG, Gaynes RP. An overview of nosocomial infections, including the role of the microbiology laboratory. *Clin Microbiol Rev*. 1993;6:428-442.
39. Pépin J, Valiquette L, Alary ME, Villemure P. *Clostridium difficile*-associated diarrhoea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ*. 2004;171:466-472.
40. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet*. 2005;366:1079-1084.
41. McDonald L C, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996–2003. *Emerg Infect Dis*. 2006;12:409-415.
42. Kuijper EJ, Coignard B, Tull P. Emergence of *Clostridium difficile*-associated disease in North America and Europe. *Clin Microbiol Infect*. 2006;12 Suppl 6:2-18.
43. Kuijper EJ, Coignard B, Brazier J, S., Suetens C., Drudy D., Wiuff C., Pituch H., Reichert P., Schneider F., Widmer A. F., Olsen K. E., Allerberger F., Notermans D. W., Barbut F., Delmee M., Wilcox M., Pearson A., Patel B. C., Brown D. J., Frei R., Akerlund T., Poxton I. R., and Tull P. Update of *Clostridium difficile*-associated disease due to PCR ribotype 027 in Europe. *Euro Surveill* 2007;12;E1-E2.
44. Barbut F, Mastrantonio P, Delmee M, Brazier J, Kuijper E, Poxton I. Prospective study of *Clostridium difficile* infections in Europe with phenotypic and genotypic characterisation of the isolates. *Clin Microbiol Infect*. 2007;13:1048-1057.
45. Wenzel RP, Thompson RL, Landry SM, Russell BS, Miller PJ, Ponce dL, et al. Hospital-acquired infections in intensive care unit patients: an overview with emphasis on epidemics. *Infect Control*. 1983;4:371-375.
46. Haley RW, Tenney JH, Lindsey JO, Garner JS, Bennett JV. How frequent are outbreaks of nosocomial infection in community hospitals? *Infect Control*. 1985;6:233-236.
47. Gastmeier P, Stamm-Balderjahn S, Hansen S, Nitzschke-Tiemann F, Zuschneid I, Groneberg K, et al. How outbreaks can contribute to prevention of nosocomial infection: analysis of 1,022 outbreaks. *Infect Control Hosp Epidemiol*. 2005;26:357-361.
48. Gastmeier P, Stamm-Balderjahn S, Hansen S, Zuschneid I, Sohr D, Behnke M, et al. Where should one search when confronted with outbreaks of nosocomial infection? *Am J Infect Control*. 2006;34:603-605.
49. Hansen S, Stamm-Balderjahn S, Zuschneid I, Behnke M, Ruden H, Vonberg RP, et al. Closure of medical departments during nosocomial outbreaks: data from a systematic analysis of the literature. *J Hosp Infect*. 2007;65:348-353.
50. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis*. 2003;9:978-984.
51. van Rijen MM, van Keulen PH, Kluytmans JA. Increase in a Dutch hospital of methicillin-resistant *Staphylococcus aureus* related to animal farming. *Clin Infect Dis*. 2008;46:261-263.
52. Wulf MW, Sorum M, van Nes A, Skov R, Melchers WJ, Klaassen CH, et al. Prevalence of methicillin-resistant *Staphylococcus aureus* among veterinarians: an international study. *Clin Microbiol Infect*. 2008;14:29-34.
53. De Neeling AJ, van den Broek MJ, Spalburg EC, Santen-Verheuevel MG, Dam-Deisz WD, Boshuizen HC, et al. High prevalence of methicillin resistant *Staphylococcus aureus* in pigs. *Vet Microbiol*. 2007;122:366-372.
54. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis*. 2008;8:159-166.
55. Nordmann P, Naas T, Fortineau N, Poirel L. Superbugs in the coming new decade; multidrug resistance and prospects for treatment of *Staphylococcus aureus*, *Enterococcus spp.* and *Pseudomonas aeruginosa* in 2010. *Curr Opin Microbiol*. 2007;10:436-440.
56. Falagas ME, Bliziotis IA. Pandrug-resistant Gram-negative bacteria: the dawn of the post-antibiotic era? *Int J Antimicrob Agents*. 2007;29:630-636.
57. Giske CG, Monnet DL, Cars O. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother*. 2008 Mar;52(3):813-21.
58. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn VP, et al. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. *Am J Epidemiol*. 1985;121:182-205.
59. Emori TG, Culver DH, Horan TC, Jarvis WR, White JW, Olson DR, et al. National nosocomial infections surveillance system (NNIS): description of surveillance methods. *Am J Infect Control*. 1991;19:19-35.
60. Haley RW. Surveillance by objective: a new priority-directed approach to the control of nosocomial infections. The National Foundation for Infectious Diseases lecture. *Am J Infect Control*. 1985;13:78-89.
61. Suetens C, Morales I, Savey A, Palomar M, Hiesmayr M, Lepape A, et al. European surveillance of ICU-acquired infections (HELICS-ICU): methods and main results. *J Hosp Infect*. 2007;65 Suppl 2:171-3.
62. Wilson J, Ramboer I, Suetens C. Hospitals in Europe Link for Infection Control through Surveillance (HELICS). Inter-country comparison of rates of surgical site infection—opportunities and limitations. *J Hosp Infect*. 2007;65 Suppl 2:165-70.
63. EARSS Annual Report 2006. 2007:ISBN-13: 978-90-6960-183-0; 1-162. Available from: <http://www.rivm.nl/earss>
64. Gaynes RP, Culver DH, Horan TC, Edwards JR, Richards C, Tolson JS. Surgical site infection (SSI) rates in the United States, 1992-1998: the National Nosocomial Infections Surveillance System basic SSI risk index. *Clin Infect Dis*. 2001;33 Suppl 2:S69-77;S69-577.
65. Suetens C, Savey A, Lepape A, Morales I, Carlet J, Fabry J. Surveillance des infections nosocomiales en réanimation : vers une approche consensuelle en Europe. *Réanimation* 2003;12:205-213.
66. Fabry J, Morales I, Metzger MH, Russell I, Gastmeier P. Quality of information: a European challenge. *J Hosp Infect*. 2007;65 Suppl 2:155-8.
67. Martone WJ, Jarvis WR, Culver DH, Haley RW. Incidence and nature of endemic and epidemic nosocomial infections 1992-1996.
68. Kaoutar B, Joly C, L'Heriteau F. Mortalité et infections nosocomiales, 2000–2001. Rapport d'enquête – synthèse. 20021-4. Available from: http://www.cclinparisnord.org/ACTU_DIVERS/MortaSynthese.doc
69. Kanerva M, Ollgren J, Lyytikäinen O. Estimating disease burden of healthcare-associated infections in Finnish acute care hospitals. *Clin Microbiol Infect*. 2008;18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 19–22 April 2008;S210. Available from: http://www.blackwellpublishing.com/eccmid18/PDFs/poster_presentation.pdf
70. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J*. 2006;27:1610-1619.
71. Gastmeier P, Brauer H, Sohr D, Geffers C, Forster DH, Daschner F, et al. Converting incidence and prevalence data of nosocomial infections: results from eight hospitals. *Infect Control Hosp Epidemiol*. 2001;22:31-34.
72. Haley RW, Culver DH, White JW, Morgan WM, Emori TG. The nationwide nosocomial infection rate. A new need for vital statistics. *Am J Epidemiol*. 1985;121:159-167.
73. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. *J Hosp Infect*. 2003;54:258-266.
74. Gastmeier P, Geffers C. Prevention of catheter-related bloodstream infections: analysis of studies published between 2002 and 2005. *J Hosp Infect*. 2006;64:326-335.
75. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. 2006;355:2725-2732.
76. Gastmeier P, Geffers C. Prevention of ventilator-associated pneumonia: analysis of studies published since 2004. *J Hosp Infect*. 2007;67:1-8.
77. Masterton R, Craven D, Rello J, Struelens M, Frimodt-Moller N, Chastre J, et al. Hospital-acquired pneumonia guidelines in Europe: a review of their status and future development. *J Antimicrob Chemother*. 2007;60:206-213.
78. Lorente L, Blot S, Rello J. Evidence on measures for the prevention of ventilator-associated pneumonia. *Eur Respir J*. 2007;30:1193-1207.
79. Torres A, Carlet J. Ventilator-associated pneumonia. European Task Force on ventilator-associated pneumonia. *Eur Respir J*. 2001;17:1034-1045.
80. CDC Guidelines for prevention of healthcare-associated pneumonia 2003. *MMRW*. 2004;53:1-36. Available from: <http://www.cdc.gov/ncidod/dhqp/guidelines.html>
81. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med*. 2004;141:305-313.
82. American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA). Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med*. 2005;171:388-416.
83. Belgian Infection Control Society. Recommandations Belges pour le contrôle et la prévention des infections à *Clostridium difficile* dans les hôpitaux aigus et dans les maisons de repos et de soins. 2006.

84. Réseau d'alerte, d'Investigation et de Surveillance des Infections Nosocomiales. RAISIN. Conduite à tenir: diagnostic, investigation, surveillance, et principes de prévention et de maîtrise des infections à *Clostridium difficile*. 2006 Available from: http://www.invs.sante.fr/publications/2006/guide_raisin/conduite_clostridium_difficile.pdf
85. Department of Health HPA regional microbiology network. A good practice guide to control *Clostridium difficile*. 2007. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4115883
86. Department of Health Saving Lives: reducing infection, delivering clean and safe care. High Impact Intervention No 7. Care bundle to reduce the risk from *Clostridium difficile*. 2007. Available from: http://www.hpa.nhs.uk/infections/topics_az/clostridium_difficile/c_diff_guidelines.htm
87. Vonberg RP, Kuijper EJ, Wilcox MH, Barbut F, Tull P, Gastmeier P, et al. Infection control measures to limit the spread of *Clostridium difficile*. Clin Microbiol Infect. 2008;14 Suppl 5:2-20.
88. Kuijper EJ, Coignard B, Tull P. Emergence of *Clostridium difficile*-associated disease in North America and Europe. Clin Microbiol Infect. 2006;12 Suppl 6:2-18.
89. Pittet D. Infection control and quality health care in the new millennium. Am J Infect Control. 2005;33:258-267.
90. Wenzel RP. Health care-associated infections: major issues in the early years of the 21st century. Clin Infect Dis. 2007;45 Suppl 1:S85-8.
91. Leal J, Laupland KB. Validity of electronic surveillance systems: a systematic review. J Hosp Infect. 2008;69:220-229.
92. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med. 2006;144:309-317.
93. van Loo I, Huijsdens X, Tiemersma E, de Neeling A, Sande-Bruinsma N, Beaujean D, et al. Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. Emerg Infect Dis. 2007;13:1834-1839.
94. Patel SJ, Graham PL III. Use of molecular typing in infection control. Pediatr Infect Dis J. 2007;26:527-529.
95. Friedrich AW, Witte W, de Lencastre H, Hryniewicz W, Scheres J, Westh H, et al. A European laboratory network for sequence-based typing of methicillin-resistant *Staphylococcus aureus* (MRSA) as a communication platform between human and veterinary medicine – an update on SeqNet.org. Euro Surveill. 2008;13(19):pii=18862.
96. Cookson B, The HARMONY participants. Harmony – The international union of microbiology societies' European staphylococcal typing network. Euro Surveill. 2008;13(19):pii=18860.
97. Hallin M, Deplano A, Denis O, De Mendonca R, De Ryck R, Struelens MJ. Validation of pulsed-field gel electrophoresis and spa typing for long-term, nationwide epidemiological surveillance studies of *Staphylococcus aureus* infections. J Clin Microbiol. 2007;45:127-133.
98. Maquelin K, Cookson B, Tassios P, van Belkum A. Current trends in the epidemiological typing of clinically relevant microbes in Europe. J Microbiol Methods. 2007;69:222-226.
99. Ammon A. Molecular typing for public health purposes. Editorial. Euro Surveill. 2008;13(19):pii=18864.
100. Eurosurveillance editorial team. Public consultation on strategies for improving patient safety by prevention and control of healthcare-associated infections. Euro Surveill. 2006;11(1):pii=2870.
101. WHO, Rosenmüller M, McKee M, Baeten R (editors) Patient Mobility in the European Union. Learning from experience. 2006:1-194. Available from: <http://www.euro.who.int/Document/E88697.pdf>
102. Pittet D, Allegranzi B, Storr J, Donaldson L. 'Clean Care is Safer Care': the Global Patient Safety Challenge 2005-2006. Int J Infect Dis. 2006;10:419-424.
103. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet. 2000;356:1307-1312.
104. Sax H, Uckay I, Richez H, Allegranzi B, Pittet D. Determinants of good adherence to hand hygiene among healthcare workers who have extensive exposure to hand hygiene campaigns. Infect Control Hosp Epidemiol. 2007;28:1267-1274.
105. Simon A, Costers M, Suetens C, and the Belgian hand hygiene campaign working group. Two multifaceted countrywide campaigns to improve hand hygiene compliance in Belgian hospitals. Submitted 2008.
106. Jans B, Suetens C, De Gheldre Y, Leens E, Bogaerts P, Coignard B, et al. Small outbreaks of VEB-1 ESBL producing *Acinetobacter baumannii* in Belgian nursing homes and hospitals through cross-border transfer of patients from northern France. Poster presentation P1616, 16th European Congress of Clinical Microbiology and Infectious Diseases, Nice, France, April 1-4 2006. Clin Microbiol Infect. 2006;12:P1616 Available from: <http://www.blackwellpublishing.com/eccmid16/abstract.asp?id=50411>
107. Naas T, Bogaerts P, Bauraing C, Degheldre Y, Glupczynski Y, Nordmann P. Emergence of PER and VEB extended-spectrum beta-lactamases in *Acinetobacter baumannii* in Belgium. J Antimicrob Chemother. 2006;58:178-182.
108. Coignard B, Barbut F, Blanckaert K, Thiolet JM, Poujol I, Carbonne A, et al. Emergence of *Clostridium difficile* toxinotype III, PCR-ribotype 027-associated disease, France, 2006. Euro Surveill. 2006;11(37):pii=3044.
109. Kassis-Chikhani N, Decre D, Gautier V, Burghoffer B, Saliba F, Mathieu D, et al. First outbreak of multidrug-resistant *Klebsiella pneumoniae* carrying blaVIM-1 and blaSHV-5 in a French university hospital. J Antimicrob Chemother. 2006;57:142-145.
110. Tietz A, Frei R, Widmer AF. Transatlantic spread of the USA300 clone of MRSA. N Engl J Med. 2005;353(5):532-3.
111. Eurostat 2007.
112. The Economic Policy Committee and European Commission, December 2005.
113. Baldwin N, Gilpin DF, Tunney MM, Kearney P, Gardiner A, Hughes C. Prevalence of methicillin-resistant *Staphylococcus aureus* amongst residents and staff of nursing homes. 18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 19-22 April 2008. Clin Microbiol Infect. 2008 S416. P1454. Available from <http://www.blackwellpublishing.com/eccmid18/abstract.asp?id=69354>
114. Jans B, Suetens C, Denis O, Struelens M. The first national methicillin-resistant *Staphylococcus aureus* prevalence study in Belgian nursing homes indicates high carriage rates among residents. 16th European Congress of Clinical Microbiology and Infectious Diseases, Nice, France, April 1-4 2006. Clin Microbiol Infect. 2006;12:O316. Available from: http://www.blackwellpublishing.com/eccmid16/PDFs/clm_1426.pdf
115. Gavazzi G, Krause KH. Ageing and infection. Lancet Infect Dis. 2002;2:659-666.
116. Garibaldi RA. Residential care and the elderly: the burden of infection. J Hosp Infect. 1999;43 Suppl:S9-18.
117. Strausbaugh LJ, Joseph CL. The burden of infection in long-term care. Infect Control Hosp Epidemiol. 2000;21:674-679.
118. Drinka P, Faulks JT, Gauerke C, Goodman B, Stemper M, Reed K. Adverse events associated with methicillin-resistant *Staphylococcus aureus* in a nursing home. Arch Intern Med. 2001;161:2371-2377.
119. Suetens C, Niclaes L, Jans B, Verhaegen J, Schuermans A, Van Eldere J, et al. Methicillin-resistant *Staphylococcus aureus* colonization is associated with higher mortality in nursing home residents with impaired cognitive status. J Am Geriatr Soc. 2006;54:1854-1860.
120. Mylotte JM. Nursing home-associated pneumonia. Clin Geriatr Med. 2007;23:553-vii.
121. Kaiser State Health Facts: <http://www.statehealthfacts.org>
122. Macfarlane AJ, Godden S, Pollock AM. Are we on track – can we monitor bed targets in the NHS plan for England? J Public Health (Oxf). 2005;27:263-269.
123. Lezovic M, Kovac R. Comparison of long-term care in European developed countries to possible implementation in Slovakia. Bratisl Lek Listy. 2008;109:20-24.
124. Eriksen HM, Iversen BG, Aavitsland P. Prevalence of nosocomial infections and use of antibiotics in long-term care facilities in Norway, 2002 and 2003. J Hosp Infect. 2004;57:316-320.