Introduction

The rapid global expansion of bacteria resistant to antimicrobials is one of the most important developments in emerging bacterial diseases\(^1\). Although, the phenomenon is global, acquired bacterial resistance to antimicrobial agents is greater in developing countries, particularly in community acquired diarrhoeal and respiratory pathogens, attributed mainly to misuse of antibiotics, which in turn is due to complex socio-economic and behavioural factors\(^2\), \(^3\), \(^4\), \(^5\), \(^6\), \(^7\), \(^8\), \(^9\), \(^10\), \(^11\). In the hospitals of developing countries only a minority of the antibiotic prescriptions are based on microbiological test results and use of prophylactic antibiotics is often inappropriate\(^12\), \(^13\). However, most of these reports are anecdotal or are not representative of all countries or even the vast and heterogeneous population within an individual country\(^14\). There are some studies from South East Asia, particularly from India, on antibiotic resistance among hospital bacteria but none investigated the extent of antibiotic resistance in hospitals \textit{vis-à-vis} use or abuse of antibiotics \(^264\) - \(^274\), \(^276\), \(^277\), \(^280\), \(^281\).

Evidence from studies in developed countries suggests a relationship between antibiotic resistance and use, consistent associations between resistance and antibiotic use in hospitals, concomitant variation in resistance as antibiotic use varies, and a dose response relationship for many pathogen/antibiotic combinations\(^15\). But, because much of these studies are performed in single hospitals and confounding factors were poorly controlled, their power to distinguish associations was poor. Moreover, some studies have failed to demonstrate an association between antibiotic resistance and use, suggesting other contributing factors such as cross-transmission, inter-hospital transfer of resistance, a community contribution to resistance, or a complex relationship between resistance and the use of a variety of antibiotics. The findings suggest that antibiotic usage is the major risk factor in development of antibiotic resistance in hospitals, but the relationship can be
complex with additional factors involved, and understanding the problem of antibiotic resistance in a hospital requires knowledge of the hospital’s pattern of antibiotic use\textsuperscript{16}.

**Health Care-Acquired Infections: scale and cost**

The risk of health care-associated infections (HCAIs) in developing countries is 2 to 20 times higher than in developed countries; in some developing countries, the proportion of patients affected by a health care-acquired infection can exceed 25\%\textsuperscript{17}.

At any time, over 1.4 million people worldwide are suffering from infections acquired in hospital. Between 5\% and 10\% of patients admitted to modern hospitals in the developed world acquire one or more infections. In the United States, 1 out of every 136 hospital patients becomes seriously ill as a result of HCAIs (equivalent to 2 million cases and about 80000 deaths a year) costing an estimated US\$ 4.5 billion to US\$ 5.7 billion per year while, in England, more than 100000 cases of HCAIs lead to over 5000 deaths directly attributed to infection each year costing cost £1 billion a year\textsuperscript{17}. In Mexico, an estimated 450000 cases of HCAIs cause 32 deaths per 100000 inhabitants each year with an annual cost approaching US\$ 1.5 billion\textsuperscript{17}. HCAIs caused by multiresistant nosocomial pathogens incurs even higher cost that is too with limited treatment options because of multiresistance e.g., invasive MRSA infection\textsuperscript{18,19,20}.

**Indian scenario**

A surveillance conducted in 12 ICUs of the 7 hospitals of 7 Indian cities found 87.5\% of all *Staphylococcus aureus* HCAIs were caused by meticillin-resistant strains (MRSA), and 71.4\% of Enterobacteriaceae were multiresistant; the study concluded that HCAI rates, length of stay, mortality and bacterial resistance were high and infection control programmes including surveillance and antibiotic policies are a priority in India\textsuperscript{21}. 
In October 2004, the World Health Organisation (WHO) launched the ‘World Alliance for Patient Safety’ in response to a World Health Assembly Resolution in 2002 urging the WHO and member states to pay the closest possible attention to the problem of patient safety. The Global ‘Patient Safety Challenge’ is a core programme of the World Alliance for Patient Safety aimed at drawing attention to patient safety. The first campaign launched in 2005-06 brings together the WHO Guidelines on Hand Hygiene in Health Care with ongoing work on blood safety, injection and immunization safety, safer clinical practices, safe water, sanitation and health care waste management. The core message of the campaign is ‘simple measures save lives’ which focus on preventing HCAIs.

The second challenge, ‘Safe Surgery Saves Lives’ commenced in 2007, was formally launched on 25 June, 2008. The third Challenge, to be launched in 2010, will focus on the unprecedented spread of drug-resistant pathogens and the implications for patient safety.

Following these high profile campaigns, the issue of HCAIs in developing countries is slowly gaining importance with signs of political commitment. Over 110 WHO Member
States have now signed a national pledge to tackle health care-associated infection; India has committed to address the Health Care associated infection in the country on 14 July, 2006 (Figure 1, Figure 2).

**Figure 2 India's pledge to address HCAIs**
Developed versus developing countries: an observation and context of the current study

There are important differences between the hospitals in developing and developed countries in terms of demography (e.g., more elderly patients) and the case mix (e.g., patients with complex surgical interventions, iatrogenic immunosuppression, and multiple co-morbidities secondary to chronic diseases) requiring multiple episodes of hospital admissions over a relatively short period of times. Moreover, there are frequent movement of patients to and from community institutions (e.g., long term residential care homes and community hospitals) and hospitals blurring the distinction between community and hospital infections.

1. A large number of patients have prosthetic devices, particularly orthopaedic implants, and complex surgical interventions for conditions like cancers, solid organ transplants and haematological malignancies with prolonged life expectancy. Some of these interventions e.g., solid organ and bone marrow transplantations require immunosuppression, sometimes severe. Multiple episodes of hospital admissions for various clinical reasons/complications are common. Also, there is a large population of patients world are elderly and have chronic diseases requiring multiple hospital admissions during their life time.

2. A vast number of elderly and vulnerable patients live in residential care homes; consequently, there is frequent transfer of patients to and from the hospital and these community institutions.

3. Many medical interventions now take place within the community set up whether general practitioner’s clinic, patients own home or residential care homes. As a result infections secondary to medical interventions occur both in the hospital and community, and the term ‘healthcare associated infections’ (HCAIs) aptly applies.
There are a number of implications of these factors in relation to HCAIs. Firstly, the hospitals no longer remained as a unique niche for multidrug resistant nosocomial pathogens - a large proportion of patients colonised or infected with multidrug resistant nosocomial pathogens now live in the community and freely move to and from community and hospitals (including inter hospital transfers). The boundary of nosocomial pathogens consequently has blurred.

Secondly, old age, severity of immunosuppression and presence of prosthetic devices influence the intensity and choice of antimicrobial therapy for an infectious episode. Frequently, more intense antimicrobial therapy is required, whether empirical or based on culture and sensitivity results.

Thirdly, therapy is often required against pathogens that are of no consequence in a normal host or in absence of a prosthetic device.

In contrast, despite continued advances, solid organ transplantation and prosthetic implants are not commonplace in the developing countries. Population is relatively younger and residential care homes for old people are very few and far between as of now. Therefore, hospitals still remain a unique niche for multidrug resistant nosocomial pathogens. Resistance to antimicrobials even of typical nosocomial pathogens but of community origin is still likely to be low. In addition, there is no or only a rudimentary infection control programme in operation in most hospitals in the developing countries. Moreover, lack of adequate hand hygiene facilities and awareness of HCAIs contribute to widespread cross-transmissions of nosocomial pathogens within the hospital. Also, in most hospitals there is no antibiotic policy, and empirical use of antibiotics is often ‘inappropriate’. It is also likely that high cost of newer antimicrobials adversely impacts adequate dosing and duration of therapy. Therefore, the total consumption of antibiotics in the hospitals in the developing countries is likely to be comparatively less despite ‘inappropriate’ usage.
There are few studies that consider these differences to address how these factors may have influenced the dynamics of emergence and spread of bacterial resistance hitherto in the developing countries. The current study aims to explore and test some of these anecdotal observations made in this section.

**Aims and objectives**

The objective of the present study is to gain epidemiological insight into the extent of the problem of multiresistance in nosocomial bacterial pathogens, in particular, *Staphylococcus aureus* and species of the Enterobacteriaceae in the Guwahati Medical College Hospital by characterising the phenotypic and molecular characteristics (in case of *S. aureus*) of the pathogens vis-à-vis risk factors such as demographic factors, exposure to antimicrobials and surgery for acquisition of meticillin resistant *S. aureus* (MRSA) and ESBL-producing Enterobacteriaceae.

Total amount and pattern of usage of antimicrobials will be calculated and compared with that of a district general hospital in England. Facilities for infection control and actual practices in the hospital will be reviewed to shed light on the transmission dynamics of nosocomial pathogens within the hospitals vis-à-vis amount and pattern of usage of antimicrobials.

Extensive literature review will be carried out to shed light on the characteristics of the local strains of *Staphylococcus aureus* and species of the Enterobacteriaceae in reference to antibiotic resistance.

It is envisaged that due to limitations of resources and access to laboratory facilities, molecular typing of *Staphylococcus aureus* would be limited to PFGE; in case of Enterobacteriaceae only phenotypic characterisation would be possible. Therefore, reliance would be placed on the current literature to predict or interpret the molecular characteristics (genotypes) from the phenotypic characterisations.
We hypothesise that resistance to antimicrobials in the nosocomial strains circulating in the hospital would reflect natural evolution based on local factors in keeping with the species specific characteristics rather than introduction of novel multi-resistant strains into the hospital which have spread and become prevalent, and that the hospital is a niche for evolution of multidrug resistant nosocomial pathogens; in contrast, isolates of community origin would likely be sensitive to a wide range of antimicrobials.

The final objective of the study is to provide certain recommendation, based on the study results, to control the menace of nosocomial infections in the hospital.