

12%*

*of all human infectious diseases are classified as re-emerging diseases (WHO, 2003)

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**New Product Training for R-Biopharm's
International Business Partners 2008**

Nosocomial Infections and Emerging Diseases

Dr. Reinhard Böhmer / Dr. Tiller Medical Laboratories

Dr. Böhmer is a leading medical microbiologist and medical director in one of the biggest German laboratories. Formerly he was attached to the Munich Bogenhausen hospital and also in South Africa. Dr. Böhmer was invited to the R-Biopharm Distributor meeting in Starnberg 2008 to conduct a training on hospital acquired infectious diseases, laboratory diagnostic requirements and hospital-related cost analysis.



Introduction

By definition, nosocomial Infections (NIs) occur in patients after admission to a hospital or healthcare service unit. NIs are considered as such if they first appear 48 hours or more after hospital admission or within 30 days after discharge (Nosocomial infections = synonym: Healthcare-associated infections).

The problem occurs worldwide in any large sized hospital. The prevalence is much lower in community hospitals.

Differences in rates appear to be due to greater severity of diseases in patients (e.g. weakened immune status) in academic hospitals and everywhere where antibiotics are given in larger volumes.

Basically, NIs are of increased public awareness because they may even be more alarming as antibiotic resistance spreads. The most common NIs are related to the

- urinary tract
- lower respiratory tract
- postoperative wounds/infections
- primary septicaemia

Incidence and cost

Healthcare costs related to the NIs are incredibly high. **Germany** has approx. 75000 sepsis cases annually at costs of 1.7 billion €, at a third of the budget of the total intensive care (ICU) medicine. 128.000 post-operative wound infections cause 1 million additional hospital days annually.

In the **USA** it has been estimated that as many as one in ten hospitalized patients acquires a Nosocomial infection (~2 million patients a year). Annual costs range from \$ 4.5 – 11 billion or contributed to 88000 deaths (data from 1999).

France has a prevalence of NIs up to 7.5 %. An estimated 5 – 19 % of hospitalized patients are infected and up to 3 % in ICUs. Patients with a NI remain in hospital for an average of 4 – 5 days additional days.

Italy: 6.7 % of hospitalized patients are infected (up to 700000 patients annually). Extrapolations assume that 70000 hospitalized patients are affected in **Switzerland**.

Australia reported out of 6 million hospital admissions per year a rate of 5 % NIs. From a total of 7000 *Staphylococcus aureus* bacteremias, 4500 are healthcare related. The average mortality rate is of 25 %.

- Tuberculosis
- Influenza
- Chikungunya
- Entamoeba
- Clostridium difficile
- Norovirus
- Giardia lamblia
- Cryptosporidium

Emerging Infectious Diseases*

Preventive actions

As many as 92 percent of deaths from hospital infections could be prevented. Main actions in hospital settings are

- Microbiological rapid diagnostics
- Screening of patients
- Surveillance of nosocomial infections
- Availability of regional epidemiological data
- Antibiotic audits in combination with reduction of antibiotic use
- Thorough hand washing and use of alcohol rubs by all medical personnel before patient contact.

Emerging infectious diseases and causative pathogens

According to the NIH (National Institutes of Health, USA) statistics, infectious diseases remain among the leading causes of death worldwide because of emergence of new diseases, re-emerge of “old” infection disease and persistence. Many important infection diseases are not adequately controlled.

Even new common drugs such as **TNF-alpha blockers** raise the risk of infections due to decreased T-cell activity. **Tuberculosis**, **Chikungunya** and influenza are emerging not locally but spreading worldwide. For **Norovirus**, Germany reported week 1 – 20, 2008 148923 cases (Robert-Koch-Institute, www.rki.de).

The epidemiology of **Clostridium difficile (C.diff.)** associated disease is changing, with evidence of increased incidence and severity particularly in ICU settings. Superinfection

with *C. diff* is a consequence of alteration of bowel flora by antimicrobial therapy. A number of countries do have guidelines for implementation of interventions to control in healthcare facilities. 3 – 7 % of diarrhoea cases in hospitals are related to *Clostridium difficile*.

During the past 2 decades, **Giardia lamblia** infection became recognized as one of the most common cause of waterborne disease worldwide. This might result from human actions such as improper disposal of sewage wastes or be due to weather and climate events, temperature affects their growth and survival.

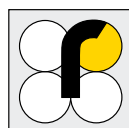
50 million cases of amoebiasis annually with estimated 40 to 50000 deaths are caused by **Entamoeba histolytica**.

Prognosis

Many of the factors promoting infections in hospital have been identified and measures of control have been developed. Infections disease specialists and medical microbiologists are worldwide hunting for the determination of infectious disease epidemiology.

Rapid near-patient diagnostics and influencing hospital personnel to carry out control measures and restraint in the use of antibiotics remains a major challenge.

* Lit.: www3.niaid.nih.gov/research/topics/emerging/list.htm



Evolution of Infectious Diseases: Emerging and Re-Emerging Pathogens

Pathogenic microorganisms have repeatedly altered the course of human history. For example, the influenza pandemic between 1918 and 1920 resulted in an estimated 70 million deaths worldwide. Even today, the overall burden of infectious diseases remains high with an estimated 26 % of deaths worldwide.

In 2003 WHO recorded more than 1400 species of infectious organisms known to be pathogen to humans.

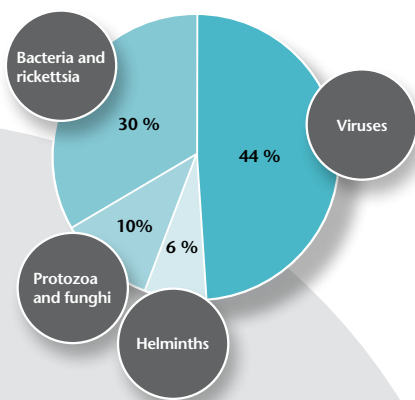
Whilst many of these organisms are associated with diseases that have been known for many years, a small but significant percentage are associated with emerging diseases, such as AIDS, Ebola and SARS.

Investigating the history of many diseases demonstrates clearly that the evolution of both humans and pathogens is interlinked. Human migration has disseminated infectious diseases or brought people into contact with new pathogens. Global environmental change has expanded the range of known pathogens or created the conditions for indigenous micro-organisms to emerge as significant human pathogens.

Emerging pathogens are those that have appeared in a human population for the first time, or have occurred previously but are increasing in incidence or expanding into areas where they have not previously been reported.

Re-emerging pathogens are those whose incidence is increasing as a result of long-term changes in their underlying epidemiology.

*Distribution of 175 Emerging Pathogenic Species**

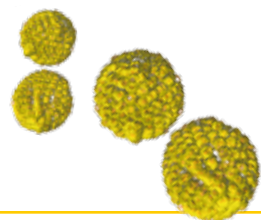


By these criteria, 175 species of infectious agents from 96 different genera are classified as emerging pathogens.

Improved methods of surveillance, epidemiological studies and the continuous development of more advanced methods of diagnosis have allowed to detect new pathogenic species of micro-organisms or to associate a known microorganism with a new or atypical set of disease symptoms. Furthermore, the agents of several diseases that were thought to have been controlled are re-emerging as a result of adaptive change in the pathogen, changes to the immunological status of the host, or environmental, demographic and socio-economic changes. Each of these pathogens represents a public health problem.

Since 1970, several species of micro-organisms from human and animal faeces and from environmental sources, including water, have been confirmed as pathogens. Examples include Cryptosporidium, Legionella, E.coli O157, Rotavirus, Hepatitis E virus and Norovirus.

R-Biopharm's intention is to help in building up an effective surveillance as well good management system for hygiene measures and for suitable therapy and prevention. Development of fast and reliable test systems for identification of emerging and re-emerging pathogens as well toxins and residuals in food and feed stuffs is one of the company's core competencies. R-Biopharm stands for a healthy environment that has to be protected.



* WHO 2003: Emerging issues in water and infectious diseases.

Are Noroviruses Emerging?

Epidemic and sporadic gastroenteritis is an important public health problem in both high income and low-income countries. In the last 30 years, several viruses have been identified as etiological agents of gastroenteritis in humans.

Outbreaks of gastroenteritis may be caused by rotaviruses, astroviruses, adenoviruses and the human caliciviruses. The human caliciviruses are assigned to two genera, the Norovirus and Sapovirus. The Norovirus cause illness in people of all age groups, whereas the Sapovirus predominantly cause illness in children. Epidemic viral gastroenteritis or "winter vomiting disease" was described as early as 1929 but it took over 40 years to the discovery of the Norwalk virus using immune electron microscopy in faecal samples in 1972. These specimens were collected during an outbreak of acute gastroenteritis which occurred in 1968 in an elementary school in Norwalk, Ohio, USA.

Europe: Increase in reported number of Norovirus outbreaks

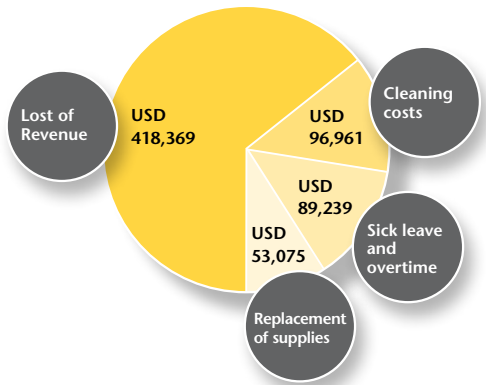
Since the summer 2006, several EU countries have faced an increase in reported number of Norovirus outbreaks or confirmed cases. In many countries, the outbreaks have hit severely in hospitals and other public settings. Two novel virus strains of GII.4 seem to circulate across Europe. (ECDC, European Centre for Disease Prevention and Control). Emerging diseases have a significant impact on morbidity and mortality (Robert-Koch-Institut, Berlin: 48 reported deaths in 2007 caused by Norovirus).

Unites States: More than 1,000 acute gastroenteritis outbreaks

Noroviruses are enterically transmitted and are a frequent cause of acute gastroenteritis, affecting 23 million people annually in the United States. CDC solicited information from the health departments all over the United States. They reported a total of 1,316 acute gastroenteritis outbreaks with onset during October-December 2006; a median of 50 % occurred in long-term-care facilities. (CDC, Centers for Disease Control and Prevention)

Outbreak cost analysis

"Outbreak costs analysis in a 1,000-beds hospital" (Johnston et. al 2007)

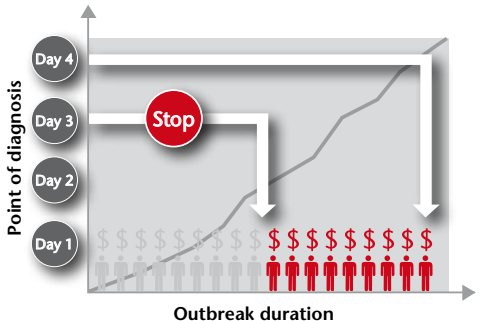


Recent studies on the socio-economic burden have analyzed the cost in health care settings. A study described a Norovirus outbreak and its control in a tertiary care hospital in the U.S. This study determined outbreak costs, including the estimated lost revenue associated with unit closures, sick leave, and cleaning expenses.

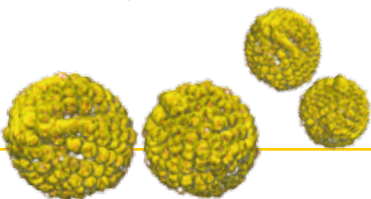
The total estimate of economic impact of this outbreak on this hospital was \$ 657,644 (Johnston et al 2007).

Timely clinical testing

The most useful measures are early diagnosis followed by the appropriate hygiene interventions.



For instance, diagnosis within three days instead of four days of the first case reduces outbreak duration by seven days (Lopman et al. 2004).



The fundamental question remains – Are Noroviruses emerging? Before we can answer to this question, what does emerging disease mean? According to World Health Organization (WHO): “An emerging disease is one that has appeared in a population for the first time, or that may have existed previously but is rapidly increasing in incidence or geographic range.” Both incidence and geographic range increased in the last couple of years. The increased detection of Norovirus is a result of better application of

improved diagnostics. Thus, this is leading to higher numbers of Norovirus cases. However, as described new circulating Norovirus strains are emerged worldwide. So, we can answer this question very clear. Yes, Noroviruses are emerging!

Second, a timely clinical testing as close as possible to the patient helps tremendously to reduce the amount of affected people and therefore also the overall expenses on the health care system.

In summary, don't waste time – Rapid diagnostics for Gastroenteritis

One, two or three bugs – It doesn't matter!

Emerging pathogens have repeatedly determined the human history. In 2001, infectious diseases accounted for an estimated 26 % of deaths worldwide¹.

Or in other words, 1415 species of infectious organisms are known to be pathogenic to humans, 12 % were associated with diseases considered to be emerging². Nowadays, emerging diseases are connected with increase mortality; increase length of hospital stay and the burden on health care costs.

R-Biopharm has launched a group of new and unique RIDA®QUICK tests for the rapid diagnosis of gastroenteritis. These rapid assays can be used to detect four emerging diseases causing gastroenteritis: Norovirus, Verotoxin/O157 Combi and Cryptosporidium/Giardia/Entamoeba Combi, in human fecal samples. Especially the time-to-result and time-to-report is critical for highly

contagious pathogens like viruses. Detection of Norovirus is of particular concern due to a rapid increase in its activity in Europe and the United States. Thus, a rapid diagnostic strategy combined with appropriate infection control measures can help duration and number of infected people³. The results help to investigate and prevent Norovirus outbreaks.

The new RIDA®QUICK assays are quick and easy to perform. Sensitive and specific results are read visually in less than 20 minutes.

These patient-near tests are made not only for microbiology laboratories but are also suitable for nursing homes, because there is no need for special laboratory equipment.



12%

For more information visit www.rapid-diagnostics.info

4 New Tests for Emerging Pathogens:

- RIDA®QUICK Norovirus
- RIDA®QUICK Verotoxin / O157 Combi
- RIDA®QUICK Cryptosporidium / Giardia / Entamoeba Combi
- RIDA®QUICK Entamoeba



New.

Unique.

Rapid.

¹ Kindhauser MK, WHO 2003.

² Taylor et al., Philosophical Transactions of the Royal Society, 2001.

³ Are Noroviruses Emerging? R-Biopharm News, 11/2008.

New Product Training for R-Biopharm's International Business Partners 2008

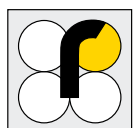


To improve our service and business partners product knowledge, a distributor meeting is organized all two years. The June 2008 event was located in Starnberg, south Germany nearby the Alps. As many as 50 participants received an intensive 3-days training session. Of course our most successful performing partners for the past two years were awarded:

1. **Avicena Diagnostica Macedonia**
(Mrs Aleksandra Tasevska)
2. **R-Biopharm France**
(Mr Marcel Bony and Mr François Gnemmi)
3. **Al-Suwaidi Trading Qatar**
(Mr Emam Khalil).

Main Topics of the meeting:

- New RIDA®QUICK products to be launched in 2008 such as Norovirus rapid, Verotoxin/O157 Combi rapid, Cryptosporidium/Giardia/Entamoeba Combi rapid and Entamoeba rapid
- Allergy diagnostic tools made by our customers. Most of our allergy products are produced according our customer's demands. We are in contact with allergy specialists worldwide.
- Details of the so-called Emerging and Re-Emerging Infectious Diseases and hospital acquired diseases (nosocomial diseases). R-Biopharm's R&D activities are focussed on this growing diagnostic market.
- New web page training: We do provide the utmost product data such as package inserts in various languages as well as performance data at www.r-biopharm.com
- R-Biopharm's engagement into fighting against colon cancer: New RIDASCREEN® ELISA products for Haemoglobin and Haemoglobin/Haptoglobin Complex as well as a new safe, clean and easy-to-use stool collection tube is launched.



Product Updates

Why not in one step?

Detection of Cryptosporidium, Giardia and Entamoeba made by R-Biopharm. Please ask your local representative to get a copy of scientific presentations.



New!

New RIDASCREEN® Stool Tube (Art. No. GZ 3002) for simple and clean collection of stool samples and speed up of stool extraction. It optimizes the test procedure to a coefficient of variation nearly 4 %. No centrifugation required, tubes can be used directly in ELISA microplate processors. A sophisticated buffer composition protects hemoglobin to ensure a stability up to three days.



Unique!

Has many promising clinical data: The unique and innovative RIDA®QUICK Verotoxin/O157 Combi test that allows simultaneous colour-differentiated detection of verotoxin and/or E. coli O157.



Screening of 32000 stool samples.

Faecal occult blood: Screening of 32000 stool samples with RIDASCREEN® Haemoglobin and RIDASCREEN® Haemo-/Haptoglobin ELISA. A number of studies conducted by R-Biopharm will combine the new diagnostic tool with colonoscopic data.



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