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Melamine contamination of dairy products in China – public health impact on citizens of the European Union

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On 10 September 2008, ProMED issued a request for information concerning 14 cases of kidney stones in infants hospitalised in Gansu province, China, in the previous two months [1]. On 21 September, Chinese authorities reported 39,965 cases of kidney stones in infants, including three deaths related to the consumption of melamine-contaminated powdered infant formula. On that day, 12,892 of them were hospitalised, 104 with severe illness. Most of these cases (82%) affected children under two years of age.

A large melamine contamination of milk-containing products, including infant formula, was reported from China. The level of contamination is variable but reaches high levels among certain producers. Contaminated food items include infant formula, liquid milk, frozen yoghurt dessert, coffee creamer, ice-cream, chocolate cookies and candies [2,3].

Food safety agencies in Hong Kong and Taiwan as well as in several other countries and locations have identified locally sold contaminated products originating from China, including: Singapore, New Zealand, Indonesia, South Korea, Vietnam and Canada [4]. Contaminated products were also exported to Bangladesh, Burundi, Myanmar, Gabon and Yemen. Media in the European Union (EU) have reported that milk products originating from China had been found in Spain and Portugal [5,6]. Ireland has withdrawn confectionary from sales outlets that had been identified by New Zealand health authorities as contaminated [7]. On 17 September, China recalled tons of milk powder produced by Sanlu Group Co since March 2008.

The importation in the EU of milk products from China has been prohibited under EU legislation since 2002. However, certain amounts of composite products (i.e. products which contain a processed product of animal origin and a product of non-animal origin) containing processed milk components may have reached the EU in the past, including confectionary, biscuits, chocolate, toffee or cakes.

On 26 September 2008, the European Commission extended this ban to all Chinese composite products containing milk or milk products, primarily intended for infants and young children, which could contain traces of milk powder [8]. As a result, systematic tests (threshold 2.5 mg/kg) will be performed on Chinese products containing more than 15% of milk products, and on all consignments of such composite products whose amount of milk product content cannot be established. The tolerable daily intake (TDI) of melamine is 0.5 mg/kg body weight in the EU [9]. Repeated exposures above the TDI require a more detailed assessment of all the data to determine the possibility of adverse effects on health.

Effects of melamine on health

Melamine, when associated with cyanuric acid [10], can cause renal failure by the formation of insoluble melamine cyanurate crystals in renal tubules and/or the formation of calculi in kidneys, ureter, urethra or the urinary bladder. These calculi are a mixture of melamine, protein, uric acid and phosphate and as such are distinct from other kidney stones. They are radiolucent and give a negative image on urinary tract X-ray. Usually both kidneys and ureters are affected. In severe cases, ultrasound investigation reveals bilateral renal enlargement (due to renal tract obstruction) with increased echogenicity. Furthermore, the urine sediment crystals may contain material with a characteristic double refraction in microscopy. Further details on differential diagnosis and ultrasound and x-ray findings can be found on the WHO webpage (http://www.who.int/csr/don/2008_09_29a/en/index.html)

Although there is evidence for the carcinogenicity of melamine under conditions that produce bladder calculi in animals, this evidence is still lacking in humans [11].

The following symptoms have been observed in infants affected by the melamine-contaminated infant formula in the current outbreak in China [12]:

- Unexplained fever arising from urinary tract infections/ bacteraemia secondary to urine stasis resulting from urinary tract obstruction;
- Unexplained crying in infants, especially when urinating, possible vomiting;
- Macroscopic or microscopic haematuria;

- Acute obstructive renal failure: oliguria or anuria;
- Dysuria (pain on urinating) and passage of stones while urinating (for example, a baby boy with urethral obstruction with stones normally has dysuria);
- High blood pressure, oedema, pain over the kidneys.

Urolithiasis (kidney stones) in infants is a very uncommon disease. However, the information available in the EU indicates that although several hundred cases of urinary stones possibly occur every year in the EU in children under the age of five years, these are almost certainly unrelated to melamine exposure.

Assessment for exposure of EU citizens through food products

The European Food Safety Authority (EFSA) published a statement on 24 September [13] indicating that the estimated exposure does not raise concerns for the health of adults in Europe should they consume chocolates and biscuits containing contaminated milk powder. Children with an average consumption of biscuits, milk-toffee and chocolate made with such milk powder would generally not exceed the tolerable daily intake (TDI), either. However, in a worst case scenario, with the highest level of contamination, children with high daily consumption of milk-toffee, chocolate or biscuits containing high levels of milk powder would exceed the TDI. Children who consume both such biscuits and chocolate could potentially exceed the TDI by more than three-fold. However, EFSA noted that it is presently unknown whether such high level exposure scenarios may occur in Europe.

In the view of the European Centre for Disease Prevention and Control (ECDC), the risk would be higher for children if counterfeit or illegally imported milk products were present in the EU. The risk for humans with compromised renal function or haemo-concentration associated with absorbing "acceptable" melamine doses, i.e. at the TDI, is unclear. Such individuals would be advised to avoid consumption of suspect products.

In particular, specific groups of EU citizens may have been and/or still be at higher risk of having been exposed to contaminated products:

- Visitors to China in the recent months;
- Citizens of overseas territories, to which contaminated products have been exported;
- Children who have been recently adopted from China and were exposed to contaminated infant formula of Chinese origin provided they are still exposed to infant formula originating from China;
- Travellers to and residents in China; they should currently be aware of the possibility of contamination of dairy products still sold in China, including milk, milk products and infant formula until the extent of the contamination is fully ascertained by Chinese authorities.

Assessment of public health impact of potential exposure

Even though there were indications of potential contamination already in late 2007, the period of potential exposure can be considered to have started in March 2008, when the contaminated batches were produced which triggered the alert. The assessment of the public health impact of potential exposure of EU citizens to melamine-contaminated food products during this period should therefore focus on children under the age of 10 years (the oldest case reported in Hong Kong) even though most of the cases were younger than three years. The ECDC suggests the assessment to be done as follows:

- Retrospectively, by checking hospital discharge data (or other appropriate sources e.g. emergency consultation registers) for ICD 10 codes related to renal failure and urolithiasis, for infants under the age of 10 years, as most cases in China were in this age group. The relevant ICD 10 codes include N17, N19, N20, N21 and N23. This review should cover the period from March 2008 onwards. Data retrieved should be compared to historical baseline data;
- Prospectively, by informing health care providers in paediatric wards of the clinical presentation of the disease. Children, under the age of 10 years, who present with symptoms or signs of urolithiasis or acute renal failure and for whom other potential causes of kidney stones have been excluded by differential diagnosis, should be tested for melamine exposure using a food exposure questionnaire and, if appropriate, by testing for melamine; confirmed cases should be notified to the health authorities.

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Community-wide outbreak of hepatitis A in Latvia, in 2008

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Since November 2007, an increase in the number of reported hepatitis A cases has been observed in Latvia. The aim of this report is to provide an update on the descriptive epidemiology of hepatitis A in Latvia and suggest some possible explanations of the recent increase in incidence.

Methods

Hepatitis A is a disease under mandatory notification in Latvia. Cases of hepatitis A are notified by health care practitioners including general practitioners and clinicians working in hospitals as well as by laboratories.

A probable case is defined as any person with a discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting) and at least one of the following three: fever, jaundice, elevated serum aminotransferase levels, and with an epidemiological link with a confirmed case. A confirmed case is defined as any person meeting the clinical and the laboratory criteria – detection of IgM antibodies against hepatitis A virus (IgM anti-HAV positive). The case definitions used are based on the European Union case definitions [1].

All notified hepatitis A cases are subject to epidemiological investigation. Epidemiologists of local branches of the Latvian Public Health Agency (PHA) interview patients or their relatives, and visit places of work or study of the patients (kindergartens, schools, food enterprises, etc.) to collect epidemiological information and organise control measures. Epidemiologists also perform investigation in any other place if two or more hepatitis A cases are epidemiologically linked to it.

Results

From 1990 to 2007, the incidence of hepatitis A in Latvia had been declining (Figure 1). The last community wide outbreak of hepatitis A in Latvia was registered in 1988–1990 with almost 20,000 cases reported during three years. Since then the number of hepatitis A cases steadily declined over the next eight years, and remained at a very low level between 2000 and 2007 (mean 87, range 15-237). The decrease of incidence of hepatitis A can be explained primarily by the overall improvement in hygiene.

In 2007, only 15 cases were registered (22 cases according to the date of onset); 8 of them imported. However, since October 2007, an increase in hepatitis A cases has been observed. Between 1 January and 24 September 2008*, a total of 759 confirmed cases of hepatitis A have been notified in Latvia (Figure 2). Additionally, five cases were exported to Estonia, one to Lithuania, one to Germany and one to Denmark.

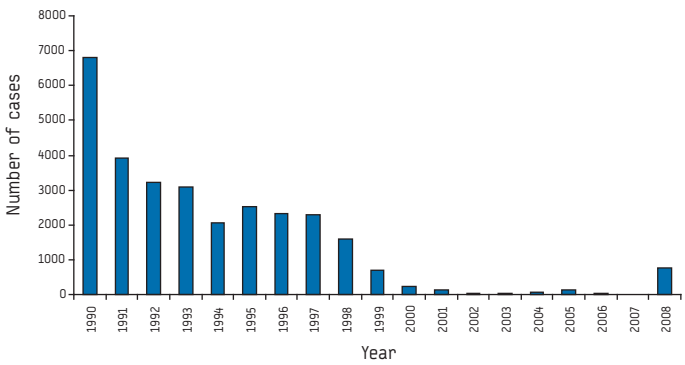
The incidence of hepatitis A increased especially intensely at the end of August – beginning of September and continues to grow. Only on 24 September*, 285 suspected cases of hepatitis A were under investigation.

Of the 759 confirmed cases reported in 2008, 706 (93%) were treated in hospitals. Five cases were fatal, all in women (age range 25-45 years, average 35). All death cases occurred in patients with underlying diseases.

The highest incidence of hepatitis A was observed in the age group 18–29 years (Figure 3). During the first seven months of

Figure 1

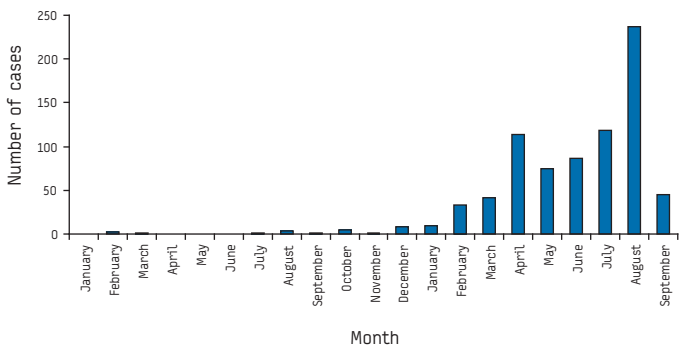
Reported number of cases of hepatitis A in Latvia, 1990 – 2008 (as of 24 September 2008)



Note: The number of cases in 2008 does not include the 285 suspected cases which are currently investigated (as of 24 September)

Figure 2

Distribution of confirmed cases of hepatitis A in Latvia in 2007 and 2008, by month of onset (n=22 in 2007, n=759 in 2008)



Note: the number of cases in September 2008 does not include the 285 suspected cases which are currently investigated (as of 24 September)

2008, the majority of hepatitis A cases occurred in males (65% of all cases); while in August the numbers of cases among males and females were equal (Figure 3). Among 639 confirmed cases in adults, 287 (45%) were in patients who were unemployed or pensioners.

The majority of the cases reported in 2008 were registered in the capital city of Riga (598 cases) and in the Riga region (73 cases).

Since December 2007, 108 cases of hepatitis A were registered among intravenous drug users (IDUs). From December 2007 till March 2008, IDUs constituted about one third of all hepatitis A cases; however, a decrease in the proportion of hepatitis A cases among IDUs has been observed in recent months because of the overall increase of cases.

In April 2008, an outbreak of hepatitis A associated with a restaurant in Riga was reported, involving 47 cases [1].

An analysis of 420 cases of hepatitis A registered in Riga during the first eight months of 2008 yielded the following results: 11 cases were connected to schools (two clusters with four and seven cases, respectively); at least 47 cases were linked to the restaurant outbreak [2]; one cluster with nine cases was registered in prison; at least 93 cases were linked to households in the community, including 26 clusters with 2 cases, 5 clusters with 3 cases, 4 clusters with 4 cases, and 2 clusters with 5 cases. In the remaining 260 cases no clear epidemiological link could be established.

No epidemiological links were identified between different clusters/outbreaks, either, but there were secondary cases, including family members of IDUs.

Genotyping has not been performed yet but is planned.

Discussion and conclusion

The following possible causes for the ongoing community-wide outbreak of hepatitis A cases in Latvia in 2008 have been suggested:

- a large number of susceptible individuals (young people) as a result of rapidly decreased exposure to hepatitis A virus;
- the initial spread of hepatitis A virus among IDUs – during the first four months of the outbreak up to 35% of cases occurred in drug users;
- a large outbreak (at least 47 cases with clinical forms of hepatitis A) associated with a restaurant;
- a considerable proportion of unemployed persons among adult cases (45%), implying low income and possibly bad living conditions; clusters of cases registered in dwelling-places of low-income inhabitants (apartment houses).

To sum up, the most likely reason for the large and still increasing number of hepatitis A cases in Latvia in 2007 is the increased susceptibility of the population, especially among young people, and the increased virus circulation in the community, which because of different routes of transmission led to community-wide spread of infection and outbreaks in different groups.

Control measures and recommendations

In Latvia vaccination against hepatitis A is recommended but not refunded within the public health system. Immunoglobulin as post-exposure prophylaxis has not been used for many years. To prevent further spread of infection, control measures are put in place in institutions at risk – educational establishments, food enterprises, social care institutions etc.

Information on preventive measures against hepatitis A is regularly disseminated via the mass media. Recommendations for inhabitants, food handlers, and staff of educational establishments have been prepared, distributed and also available on the PHA website (http://www.sva.gov.lv). Communication with school boards, Health Inspectorate, Food and Veterinary Service and other services is taking place to disseminate information and recommendations on prevention of hepatitis A. Seminars on hepatitis A prevention for healthcare workers including medical staff of educational establishments were organised. Additional control measures such as medical observation and quarantine are implemented in places at risk, including children groups in kindergartens or school classes where hepatitis A cases were registered.

It is important to further strengthen the prevention through communication with public, and to continue surveillance and control measures, as well as to perform genotyping of HAV isolates.

Exchange of information on international level is also necessary. To date eight cases of hepatitis A linked to Latvia have been registered in other European countries. We therefore consider

Figure 3

Distribution of confirmed cases of hepatitis A in Latvia, 2008, by age and sex (n = 758)

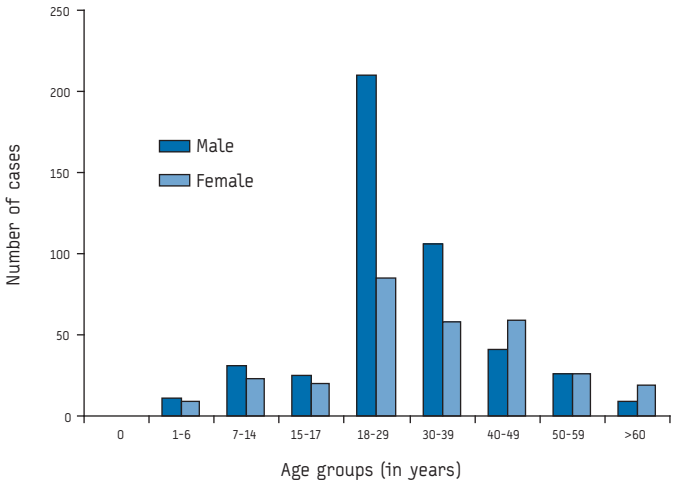
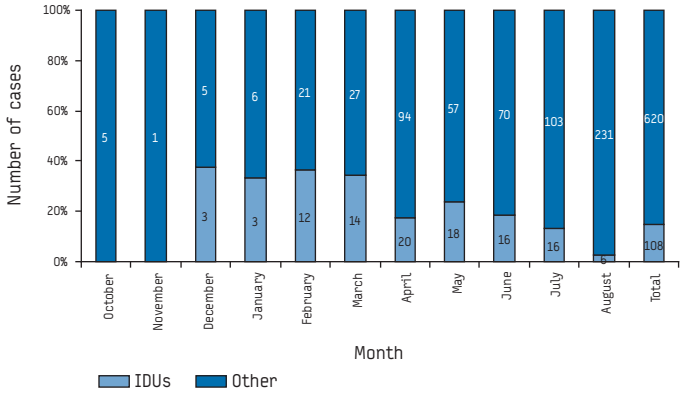


Figure 4

Proportion of injecting drug users (IDUs) among hepatitis A cases, by month of onset, Latvia, October 2007 - August 2008 (n=728)



Note: Information on cases with onset in August 2008 is not complete

that there exists a risk for international spread, especially among travellers with risk behaviour.

*Update of the situation as of 2 October: Since 24 September (analyzed in the article), the number of confirmed cases of hepatitis A has increased by 257, reaching the total of 1016 confirmed cases. Further 265 suspected cases are under investigation.

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Increase in hepatitis A cases in the Czech Republic in 2008 - preliminary report

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The public health protection authorities in the Czech Republic report a rise in cases of viral hepatitis A (HAV) since the end of May 2008. In total, as many as 602 HAV cases have been reported in 2008 until the end of calendar week 39 (28 September).

In the Czech Republic, hepatitis A is a mandatorily reportable disease and its prevention is specified in the guidelines of the Ministry of Health [1]. When suspecting or diagnosing HAV the attending physician (usually a general practitioner) refers the patient to the hospital where the patient is isolated in an infectious diseases ward. The physician reports the case to the public health protection authority without delay. All patients with suspected hepatitis A or quarantined persons are screened for diagnostic markers of HAV. The confirmed case of HAV is a case that meets the clinical case definition and is laboratory-confirmed in accordance with the European Union (EU) case definition [2].

The current situation of viral hepatitis A in the Czech Republic

Since the end of May 2008, a rise in HAV cases has been observed in the Czech Republic (Figure 1). As many as 602 HAV cases were reported between calendar weeks 1 and 39 of 2008, eight times more than in the same period of 2007 (when 75 HAV cases were reported until week 39). It is about a six-fold rise in comparison with the average number of cases reported in the same period in 2003-2007 (mean 96, range 75 - 198 cases reported).

The highest numbers of cases have been reported from two of the 14 administrative regions: Prague region with 346 HAV cases (57.5% of the reported total number of cases) and the neighbouring Central Bohemian region with 83 cases (13.8%). In the other regions, only sporadic HAV cases and small outbreaks (mainly in household clusters) have been reported, similarly as in previous years. The absolute numbers of HAV cases by region are shown in Figure 2.

Age and sex distribution

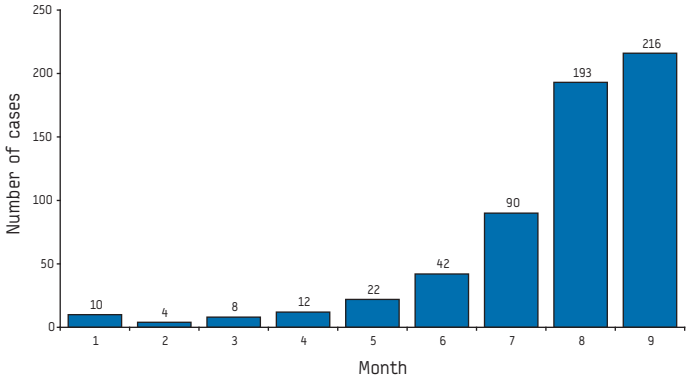
Of the total of 602 HAV cases, 364 (60.5%) have been reported in males and 238 (39.5%) in females.

As to age distribution, most (78.5%) cases have been diagnosed in patients aged from 15 to 64 years. The peak number of cases (166 cases) has been recorded in the age group 25-34 years. The most affected age group with the highest incidence rate of cases is that of 20-24-year-olds. Both the absolute and relative morbidity figures are shown in Figure 3. No death was reported.

Forty-six (7.6%) HAV cases were reported in the age group 0-14 years. An increase in HAV cases in this age group has been observed since July 2008 and is becoming more pronounced with children coming back to school in September. This is consistent with the known seasonal phenomenon of increase in HAV clusters in schools after the summer vacation. Nevertheless, this year the upward trend is expected to continue.

Figure 1

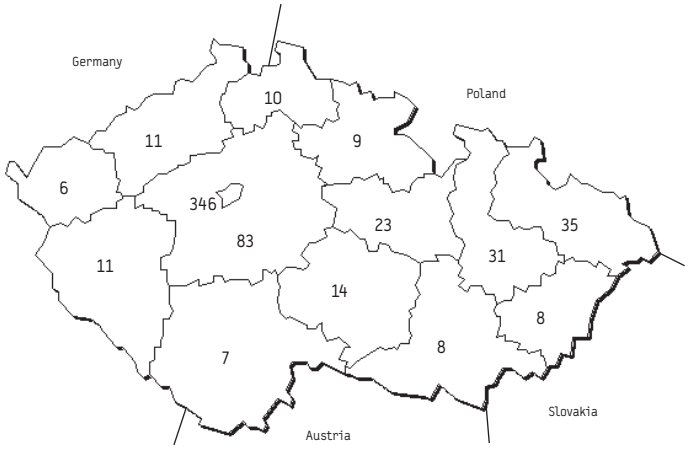
Cases of viral hepatitis A in the Czech Republic, January - September 2008 (n=602)



Note: The number of cases reported in September is not complete

Figure 2

Cases of viral hepatitis A by region, Czech Republic, weeks 1-39 of 2008 (n=602)



Risk groups

A rise in HAV cases has been observed especially since calendar week 26 (starting June 22) of 2008 when injecting drug users (IDUs) were the most affected group. Substantial increase in HAV cases among IDUs was recorded in the age group 25-34 years, in particular in the Prague and Central Bohemian regions with HAV epidemic outbreaks. Until week 39 of 2008 as many as 128 HAV cases, i.e. 21.3% of the reported total, were diagnosed in IDUs and the current situation of HAV occurrence in this group could be considered as an ongoing outbreak. The lack of hygiene is the most probable reason for person-to-person transmission in this group.

The remaining majority of 474 HAV cases occurred in the general population, in clusters (such as e.g. in prisons) and in risk groups (e.g. homeless people, alcoholics). Some of those individuals could be unidentified IDUs.

Imported cases

Investigations revealed 35 HAV cases to have been imported to the Czech Republic from other countries. Ten cases were imported from Egypt, four cases from Slovakia, three from each Croatia and Greece, two cases from each Spain, Tunisia and Turkey, and single cases from nine other countries. No case appeared to be linked to the Latvian outbreak [3,4].

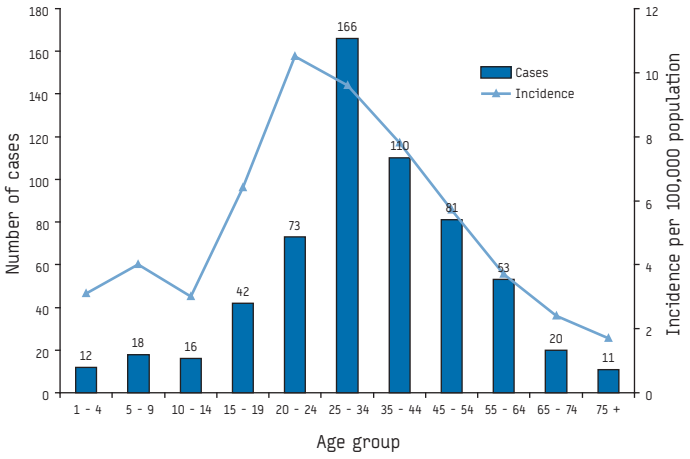
Conclusions

In the current situation characterised by a rise in HAV cases, the standard anti-epidemic measures are taken, coordinated by the Ministry of Health. They include patient isolation and quarantine, surveillance of contacts, disinfection and targeted vaccination in the outbreak areas. Post-exposure prophylaxis by vaccine was provided to HAV contacts in foci and preventive vaccination was offered to IDUs and homeless people in Prague.

HAV patients' contacts that perform activities at risk of spreading the infection (e.g. food industry) are instructed not to continue such activities and to remain under enhanced surveillance for 50 days after the last contact with the patient. The public health protection authorities issued HAV response information for school facilities and general practitioners (GPs). Information for the general public is available primarily at the websites of the National Institute of Public Health, Ministry of Health of the Czech Republic and Regional Public Health Authorities and in the mass media. Active surveillance including detailed epidemiological investigation is ongoing.

FIGURE 3

Cases of viral hepatitis A, by age, Czech Republic, weeks 1-39 of 2008 (n=602)



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Methicillin-resistant Staphylococcus aureus nasal carriage among healthy employees of the Hellenic Air Force

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The prevalence of methicillin-resistant Staphylococcus aureus nasal carriage among 959 healthy employees of the Hellenic Air Force was investigated from November 2004 to October 2005. Nine participants were found to be colonised by methicillin-resistant Staphylococcus aureus (MRSA) (SCCmec type IV). Eight of the MRSA isolates were PVL-negative and belonged to ST30 by MLST, while the remaining one isolate was PVL-positive and classified as ST-80.

Introduction

The incidence of infections caused by methicillin-resistant Staphylococcus aureus (MRSA) apparently acquired in the community (CA-MRSA) is increasing. CA-MRSA isolates are commonly non-multi-drug resistant and belong to lineages distinct from those of MRSA strains prevailing in hospitals [1]. Recent reports from Greece indicated community emergence of MRSA mainly implicated in skin and soft tissue infections in children [2,3]. Yet, the extent of the spread of CA-MRSA in the community has not been studied. We attempted to evaluate the prevalence as well as the microbiological and epidemiological characteristics of MRSA strains in a population of healthy adults in Greece.

Methodology

The study population consisted of employees of the Hellenic Air Force (HAF), residing in different geographical areas of Greece, visiting the Air Force General Hospital in Athens from November 2004 to October 2005, for a scheduled biannual medical examination. Before joining the HAF, all participants had been in good health. For operational reasons, they trained and maintained good physical fitness. Additionally, they underwent an obligatory medical examination at least once every two years. Therefore, this study population was considered as approximating "healthy adults". Demographic data and medical history over the preceding year, including hospitalisation, surgery, use of antibiotics or other medication and underlying diseases, were obtained for each participant during a short interview by a medical doctor.

Swabs obtained from both anterior nares of each individual were immediately streaked onto mannitol salt agar containing 2 µg/ml oxacillin (Oxacillin Resistance Screening Agar Base, Oxoid Ltd.). Plates were incubated at 35ºC for 48 h. Colonies demonstrating an intense blue colour were subcultured onto blood agar and incubated overnight at 35ºC. Species identification was performed by standard methods. Susceptibility profile to a wide variety of antimicrobial agents was determined by the disk diffusion method according to the current CLSI guidelines. Isolates were also tested by an oxacillin disk (1 µg) and a cefoxitin disk (30 µg) to confirm methicillin resistance. MRSA isolates were defined as community-associated according to established criteria [4].

MRSA isolates were characterised by multi-locus sequence typing (MLST) and pulsed-field gel electrophoresis (PFGE) of chromosomal DNA SmaI digests. Macrorestriction patterns were compared to previously identified clones [5]. Multi-locus sequence typing (MLST) was performed to all PFGE/SCCmec types. MRSA were additionally characterised by spa typing. Sequences of amplified parts of the spa gene were analysed using the Ridom StaphType software (Ridom GmbH, Würzburg, Germany). Detection of mecA as well as SCCmec typing was carried out by PCR. Genes lukS-PV and lukF-PV encoding Panton-Valentine leukocidin (PVL) were also identified.

Data were processed and analysed by using the SPSS statistics software, version 12 for Windows. Bivariable comparisons were carried out by the $\chi 2$ or Fisher's exact test for categorical variables and the t-test for continuous variables.

Results

A total of 959 individuals (874 males) aged 18 to 60 years (mean age 33) were enrolled in the study. Nine of the 959 participants (0.94%, 95% confidence interval [CI] 0.33% to 1.55%) were colonised with MRSA. All MRSA carriers were males. Two of the colonised individuals were smokers. One of the MRSA carriers reported systematic use of inhaled corticosteroids during the two months preceding enrolment. Another carrier had been treated with antibiotics two months prior to sampling. Three of the colonised individuals had been admitted to different hospitals at least once in the year before enrolment in the study. Two of them had been hospitalised in medical wards while the third one had been admitted to a surgical ward. In two MRSA carriers none of the investigated risk factors was identified. Among the demographic and clinical variables, prior hospitalisation and use of inhaled corticosteroids appeared to be correlated with an increased risk for MRSA colonisation ($P<0.01$) (Table 1).

Characteristics of the MRSA isolates are presented in Table 2. All nine isolates were susceptible to imipenem, gentamycin, erythromycin, clindamycin, ciprofloxacin, trimethoprim-

sulfamethoxazole, rifampicin, linezolid, teicoplanin and vancomycin. One isolate (Sa-344) was resistant to tetracycline (Tet) and two isolates (Sa-344, Sa-784) exhibited intermediate susceptibility to fusidic acid (Fus).

Eight isolates exhibited similar PFGE patterns (type A) not differing by more than three bands, correlated to ST30 by MLST. The chromosomal fingerprint of isolate Sa-344 was distinct (type C) belonging to ST80 by MLST. A total of five spa types were identified. Five of the eight ST30 isolates were classified as t012 (three strains) and t018 (two strains) that are common among strains of this ST. ST80 strain was classified as t044, a spa type strongly associated with this particular lineage. SCCmec typing revealed that all isolates possessed the SCCmec type IV. Genes lukF-PV and lukS-PV encoding PVL were detected only in the ST80 isolate.

Discussion

This study confirms the circulation of PVL-positive t044/ST80-IV which is common among CA-MRSA in Europe [6] as well as several spa variants of a PVL-negative ST30-IV MRSA frequently encountered in Greek hospitals [5]. While only one of the nine isolates belonged to ST80, this type seems to predominate among community-acquired infections requiring hospitalisation [2,3] most likely reflecting a higher virulence. In addition, since the PVL-positive strain was one of the two fusidic acid-resistant MRSA

Table 1

Risk factors tested for MRSA colonisation, study of Hellenic Air Force employees, Greece, 2004-2005 (n=959)

Characteristics	Number (%) of MRSA-colonised subjects	Total number of subjects	Statistically significant difference
Sex			P>0.05
Male	9 (1.03)	874	
Female	0 (0)	85	
Smoking			P>0.05
No	7 (1.39)	501	
Yes	2 (0.44)	458	
Antibiotic use (within the past two months)			P>0.05
No	8 (0.89)	902	
Yes	1 (1.75)	57	
Corticosteroid use (within the past two months)			
No	8 (0.85)	943	
Yes (inhaled)	1 (10)	10	P<0.01
Yes (*per os*)	0 (0)	6	
Hospitalisation (during the past year)			
No	6 (0.71)	844	
Yes (medical ward patients)	2 (6.25)	32	P<0.01
Yes (surgical ward patients)	1 (1.2)	83	

Table 2

Characteristics of nine CA-MRSA isolates from healthy carriers, study of Hellenic Air Force employees, Greece, 2004-2005

Isolate	Resistance to non-β-lactams	PFGE type (MLST)	mecA type	spa type	PVL	Factors potentially associated with MRSA colonisation
43	-	A (ST30)	IV	t1051	-	Smoking
196	-	A (ST30)	IV	t046	-	Antibiotics
344	Tet, Fus	C (ST80)	IV	t044	+	Hospitalisation (medical ward)*
408	-	A (ST30)	IV	t046	-	Inhaled corticosteroids*
714	-	A (ST30)	IV	t018	-	-
778	-	A (ST30)	IV	t018	-	-
784	Fus	A (ST30)	IV	t012	-	Hospitalisation (surgical ward)
901	-	A (ST30)	IV	t012	-	Smoking
933	-	A (ST30)	IV	t012	-	Hospitalisation (medical ward)*

* Denotes factors that appeared as significantly associated with MRSA colonisation

isolates, the emergence of MRSA with fusidic acid resistance could be a convenient means for the timely detection of any increase in the incidence of PVL-positive MRSA in the community [7].

Differences in MRSA colonisation rates of apparently healthy community-dwelling persons have been observed in various settings. In western European countries colonisation rates are comparable to the rate observed here in Greece [6]. In other countries such as Taiwan, however, the respective rate is as high as 3.5% and has been partly attributed to the excessive community use of antibiotics [8]. Although consumption of antibiotics in Greece ranks among the highest in Europe, the MRSA isolation rate in this study was relatively low. This could be partly due to the fact that the study population was composed of individuals healthier than average adults and with limited exposure to antibiotics and healthcare.

Eight of the isolates were indistinguishable from the ST30 strain that has been established in Greek hospitals [5,9]. Notably, three of the eight respective carriers had been admitted to a hospital at least once in the year preceding enrolment in the study. Hence, a hospital origin of the ST30 strains circulating in this community cannot be excluded.

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Prioritisation of infectious diseases in public health - call for comments

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In order to allocate rationally resources for research and surveillance of infectious diseases at the level of the German public health institute (RKI), we prioritised pathogens by public health criteria. After screening the relevant literature we developed a standardised methodology including a three-tiered scoring system for selected pathogens. The pathogens were rated in four categories containing a total of 12 criteria: burden of disease including incidence, severity, mortality; epidemiologic dynamic including outbreak potential, trend, emerging potential; information need including evidence on risk factors/groups, validity of epidemiologic information, evidence for pathogenesis; international duties and public attention; health gain opportunity including preventability, treatability. For each criterion a numerical score of +1, 0 or -1 was given and each criterion received a weight by which the numerical score of each criterion was to be multiplied. The total weighted scores ranged from +22.7 (influenza) to - 64.4 (cholera) with the median being -22.9 (rubella). Relevant changes were observed between weighted and unweighted scores. The chosen approach proved to be feasible and the result plausible. However, in order to further improve the methodology we invite experts to give feedback on the methodology via a structured web-based questionnaire at www.rki.de/EN > Prevention of infection > Infectious Disease Surveillance > Pathogen prioritization. Results of this survey will be included in a modification of the methodology.

Background

One of the challenges of public health is that infectious disease control covers a wide range of pathogens requiring diverse methods for prevention and control. Furthermore, infectious diseases vary greatly in occurrence, severity and other factors that make it difficult to compare the public health importance of the underlying pathogens. Resources for research, surveillance and other public health activities are limited; it is therefore of major importance to allocate rationally these resources by using public health criteria. The agendas of institutions in the field of public health and infectious diseases, however, are fragmented and experts are increasingly specialised, making it difficult to find institutions or individuals who would be able to prioritise a broad range of infectious diseases without being biased by individual professional focus on one hand or lack of specific pathogen-related knowledge on the other.

In the past decade a number of efforts have been made to prioritise systematically infectious diseases by public health criteria resulting in different outcomes depending on the objectives and methodology used [1-5]. But even prioritisation schemes with similar objectives have applied different sets of criteria as illustrated in Table 1.

In 2004 the department for infectious disease epidemiology of the Robert Koch Institute (RKI), the national public health institute in the portfolio of the German federal ministry of health, initiated a prioritisation exercise to guide the research and surveillance strategies of the department [6]. Initial findings were presented at three international scientific conferences in 2006 and 2007 [7-9].

After this a publication in a nationwide non-scientific journal [10] elicited considerable and unexpected interest from the general public and the scientific community. Therefore, as part of updating and improving the current prioritisation methodology, we would like to present this methodology also to the broader international public health community outside the RKI and Germany to collect suggestions for improvement. In the following we describe and evaluate the methodology of the prioritisation previously conducted by the RKI to provide the background information necessary for comment on our approach. We cordially invite comments on the proposed methodology via a web-based questionnaire accessible at http://www.rki.de/EN > Prevention of infection > Infectious Disease Surveillance > Pathogen prioritization.

Methodology

While preparing our exercise we analysed prioritisation efforts over the past decade by searching the literature in Medline using the search terms prioritisation OR priority AND (surveillance OR infectious diseases OR public health) and based on presentations from the EAN workshop on "New Tools for early Warning" that took place in Lyon on 6 and 7 February 2004, [1-5,18,19]. A flow chart of our methodology is presented in Figure 1.

A list of pathogens was compiled based on one or more of the following criteria: notifiable according to German law [11], reportable within the European Union according to European regulations [12], listed as chapters in selected established manuals and textbooks on infectious diseases [13-15], causative agent in outbreaks reported to RKI in the past 10 years, agent with potential for deliberate release [16]. In the following we list the pathogens but also refer to the related diseases in humans.

Every pathogen was rated according to the 12 criteria listed in Table 2. For each criterion a numerical score of +1, 0 or -1 was given as defined in Table 2. The score of +1 represented high and a score of -1 low importance with respect to a criterion. A score

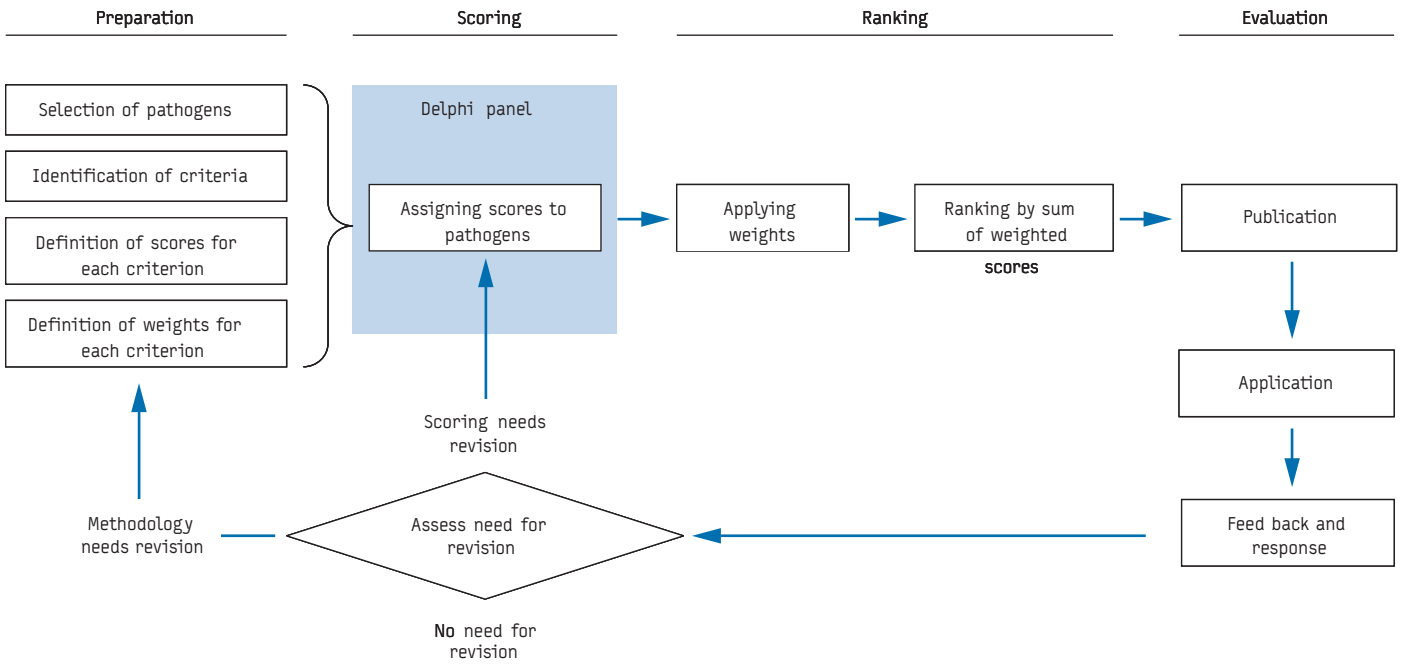
TABLE 1

Comparison of the evaluation criteria of different schemes for prioritisation of infectious diseases (the prioritisation by Reseau National de Santé Publique, 1995, France, is not included as it contained categorisation principles rather than criteria) between 1995 and 2008

Reference	Rushdy & O'Mahony 1998 (3)	Weinberg *et al* 1999 (20)	Doherty 2000 (1)	Horby *et al* 2001 (2)	Institute de Veille Sanitaire (InVS) 2001 (5)	World Health Organisation 2003 (4)	Krause *et al.* 2008 (6)
Country	United Kingdom	European Union	Canada	United Kingdom	France	South East Europe	Germany
Group of criteria	Specific name of criteria (as used in respective publications)						
International aspects and public concern	- public concern - public health laboratory service (PHLS)-added value	- international surveillance programmes	- international consideration - risk perception - potential to drive public health policy - other sector interest	-public concern	- not applied -	- not applied -	- international duties and public attention
Occurrence	- not applied -	- not applied -	- incidence	- not applied -	- epidemiology	- not applied -	- incidence
Epidemiologic dynamic	- potential threat	- not applied -	- potential spread - changing patterns	- potential threat	- not applied -	-potential threat -long term effects on communicable diseases	- outbreak potential - trend - emerging potential
Burden of disease	- burden of ill health	- not applied -	- severity	- burden of ill health	- not applied -	-disease impact -present burden of ill health	- severity - mortality
Health gain opportunity	- health gain opportunity	- not applied -	- preventability	- health gain opportunity	- prevention and control measures	-low incidence only maintained by public health activities - health gain opportunity - necessity for immediate public health response	- preventability - treatability
Socioeconomic aspects	- social/ economic impact	- collective economic impact	- socioeconomic burden	- social/ economic impact	- not applied -	-social/economic impact	- not applied -
Information need	- not applied -	- not applied -	- not applied -	- not applied -	- not applied -	- not applied -	- evidence for risk factors/ groups - validity of epidemiologic information - evidence for pathogenesis
Other	- not applied -	- not applied -	- not applied -	- not applied -	- veterinary public health	- not applied -	- not applied -

FIGURE 1

Work flow for prioritisation, Robert Koch Institute, 2008



of 0 referred to pathogens with average importance or pathogens, for which lack of knowledge or opinion of the participants in the working group did not allow a decision for one of the other two scores.

Each criterion received a weight by which the numerical score of each criterion was to be multiplied. Hence for each pathogen a sum of the unweighted and a sum of the weighted scores was generated. The weight of each criterion was determined before and independently of the categorisation for each pathogen: all participants were asked to put the 12 criteria in a sequential order with 12 being the most important and one being the least important criterion. An average was computed for each criterion, defining its weight. The total weighted score was defined as the sum of the weighted scores of all 12 categories per pathogen. These were finally normalised to the spectrum of the unweighted total scores to allow comparisons. We demonstrate the effect of weighting by presenting detailed data on the highest, lowest and median ranking pathogen as well as for the two pathogens with adjacent ranks to the median rank.

Results

The overview of prioritisation exercises in Table 3 shows that objectives, methodological approaches and especially the level of standardisation differed considerably in these efforts. Partly due to different objectives of the prioritisation, also the number and type of criteria varied. Categories used by most groups are incidence, burden of disease and opportunity for health gain [1-5], which are included in our exercise.

The working group on prioritisation consisted of eleven senior epidemiologists and infectious disease specialists at the department for infectious disease epidemiology at RKI. They categorised a list of 85 pathogens shown in Table 4.

The distribution of the normalised ranks is presented in Figure 2 and detailed scores for selected diseases are shown in Table 5. The total weighted scores ranged from +22.7 (influenza) to - 64.4 (cholera) with the median being -22.9 (rubella). The spectrum found in the total unweighted scores contained 12 possible ranks ranging from +2 to -9. Table 5 demonstrates the differences obtained from weighting for some selected pathogens.

Table 2

Criteria and definition of the respective scores for the prioritisation of pathogens, Robert Koch Institute, 2008

Criteria	Values		
	-1	0	1
Burden of disease			
Incidence	<1/100.000	1/100.000-20/100.000	>20/100.000
Severity	hospitalisation is very rare, work loss less than 2 days, no persisting handicaps	hospitalisation is rare, work loss of more than 5 days is rare, very rarely persisting handicaps	hospitalisation is frequent, work loss of more than 5 days is frequent, persisting handicaps do occur
Mortality*	<50 deaths/year in Germany	between 50 und 500 deaths /year in Germany	more than 500 deaths /year in Germany
Epidemiologic dynamic			
Outbreak potential	outbreaks are very rare	outbreaks with 5 or more cases are rare	outbreaks with 5 or more cases are frequent
Trend	diminishing incidence rates	stable incidence rates	increasing incidence rates
Emerging potential	disease already endemic or very unlikely to be introduced to Germany	disease has the potential to be introduced to Germany sporadically	disease is likely to emerge in Germany in a relevant way
Information need			
Evidence for risk factors /groups	risk factors and risk groups are identified based on scientific evidence	risk factors and risk groups are basically known but scientific evidence is missing	risk factors and risk groups are not known
Validity of epidemiologic information	epidemiologic situation is well known and scientifically valid	epidemiologic information exists but is scientifically not very valid	epidemiologic information is insufficient
International duties and public attention	no international duties or political agenda, minor public attention	no international duties but informal political expectations, moderate public attention	international duties or explicit political agendas, high public attention
Evidence for pathogenesis	information on pathogenesis and transmission routes is available and well supported by scientific evidence	information on pathogenesis and transmission routes is basically available but not well supported by scientific evidence	information on pathogenesis and transmission routes is hardly available
Health gain opportunity			
Preventability	there are hardly any possibilities for prevention or there is no need for prevention	concepts for prevention are established but there is need for further research to improve its effectiveness	strong need for further research on preventive measures because need for prevention is clear but concepts for prevention are missing
Treatability	medical treatment is rarely necessary or effective treatments are available to positively influence the burden of disease or the prognosis	medical treatment is frequently indicated but medical treatments only have a limited influence on the burden of disease or the prognosis	medical treatment is desirable but currently there is no treatment available that positively influences the burden of disease or the prognosis
Proposed alternative to mortality			
Case fatality rate*	<0,01%	0,01- 1%	> 1%

Table 3

Distribution of pathogens by total weighted and un-weighted scores during prioritisation, Robert Koch Institute, 2008

Reference	Anonymous 1995 (19)	Rushdy & O'Mahony 1998 (3)	Weinberg *et al* 1999 (20)	Doherty 2000 (1)	Horby *et al* 2001 (2)	Institute de Veille Sanitaire (InVS) 2001 (5)	World Health Organisation 2003 (4)	Krause et al. 2008
Year	1995	1997	1997	1998	1999	2000-2001	2002	2005
Country	France	United Kingdom	European Union	Canada	United Kingdom	France	South East Europe	Germany
Organisation	Reseau National de Santé Publique (RNSP)	Public health laboratory service (PHLS) Overview of Communicable Diseases Committee	Charter group of European Commission (EC)	Canadian Advisory Committee on Epidemiology	Public health laboratory service (PHLS) Overview of Communicable Diseases Committee	Institute de Veille Sanitaire (InVS)	Dubrovnik Pledge / World Health Organisation	Robert Koch Institute
Prioritisation objective	select diseases for surveillance	programme initiatives in infectious disease control	select diseases for surveillance in	select diseases for surveillance	programme initiatives in infectious disease control	prevention of non-food-borne zoonotic diseases	select diseases for surveillance	epidemiological research and surveillance
Number of diseases	84	33 (+8 generic disease groups)	26	43	58 (+11 generic disease groups)	37	53	85
Number of criteria	3 principles	5 criteria	9 criteria	10 criteria	5 criteria	> 5 criteria	8 criteria	12 criteria
Scoring system	No	5-tiered	5-tiered	3-, 4-, and 6-tiered	5-tiered	not quantifiable	5-tiered	3-tiered
Score-specific definition	no	no	no	yes	no	no	no	yes
Weighting applied	no	no	no	implicitly	no	no	no	systematically
Methodology of collecting opinion	Delphi	survey	Delphi	Delphi	survey	working group	Delphi	Delphi
Number of participants	over 50	194	14	6	518	10	not published	11
Type of participants	interministerial and regional experts	experts in communicable disease control and public health laboratory service (PHLS)	heads of national institutions with responsibilities for communicable diseases surveillance	provincial epidemiologists	different health care professionals	interministerial and regional experts	participants of World Health Organisation workshop (not published)	epidemiologists at national public health institute (RKI)

Table 4

List of pathogens selected for prioritisation, Robert Koch Institute, 2008

Adenovirus	*Escherischia coli*, shigella toxin producing (STEC/HUS)	*Leishmania* spp.	*Salmonella* typhi
Babesia microti	*Echinococcus granulosus*	*Leptospira interrogans*	*Shigella* spp.
Bacillus anthracis	*Echinococcus multilocularis*	*Listeria monocytogenes*	*Staphylococcus aureus*, methicillin resistant (MRSA)
Bartonella spp.	*Ehrlichia chaffeensis*	Measles virus	*Staphylococcus aureus*, toxigenic
Bordetella pertussis	*Entamoeba histolytica*	*Microsporum* spp.	*Streptococcus* spp. other than *Str. pneumoniae*
Borrelia burgdorferi	Epstein-Barr virus	Molluscipoxvirus	*Streptococcus pneumoniae*
Brucella abortus	*Francisella tularensis*	Mumps virus	*Toxoplasma gondii*
Bovine Spongioform Encephalitis (BSE)/ variant Creutzfeldt Jakob Disease (vCJD)	*Giardia lamblia*	*Mycobacterium* Leprae	*Treponema pallidum*
Campylobacter jejuni	*Haemophilus influenzae*	*Mycobacterium tuberculosis*	*Trichinella spiralis*
Central European tickborne encephalitis virus	Hanta virus	*Mycobacterium*, other (non-tuberculous)	*Trichomonias vaginalis*
Chlamydophila pneumoniae	*Helicobacter pylori*	*Mycoplasma* spp.	Varicella virus
Chlamydophila psittaci	Hepatitis A virus	*Neisseria gonorrhoeae*	Variola virus
Chlamydia trachomatis	Hepatitis B virus	*Neisseria meningitidis*	*Vibrio cholerae*
Clostridium botulinum	Hepatitis C virus	Norovirus	Viruses, others causing hemorrhagic fevers
Clostridium tetani	Hepatitis D virus	Parvovirus B 19	West Nile virus
Corynebacterium diphtheria	Hepatitis E virus	*Plasmodium* spp.	Yellow fever virus
Coxiella burnetii	Herpes simplex virus (HSV)	Polio virus	*Yersinia enterocolitica*
Cryptosporidium parvum	Human immunodeficiency virus (HIV)	Rabiesvirus	*Yersinia pestis*
Cyclospora cayetanensis	Human papilloma virus (HPV)	Rota virus	*Yersinia pseudotuberculosis*
Cytomegalovirus	Human T-cell lymphotrophic virus (HTLV)	Rubellavirus	
Dengue virus	Influenza virus	*Salmonella* spp. (non typhi non paratyphi)	
Escherischia coli, enteropathogenic (non STEC/HUS)	*Legionella pneumophila*	*Salmonella* paratyphy	

Discussion and conclusions

The described methodology builds on the experiences of similar efforts [1-5,18, 19] and attempts to increase the level of standardisation and transparency in prioritising pathogens based on public health criteria. In comparison to the cited prioritisation efforts, our approach may appear overly standardised. We believe, however, this ensures transparency and reproducibility, which are important, especially as prioritisation may easily affect funding and policy issues. Furthermore, our methodology allows for adaptations if certain conditions change e.g. if a vaccine becomes available or if the incidence changes significantly.

The result of the prioritisation at RKI shows a multi-modal distribution with the majority of scores below 0 indicating that, with a given definition of scores and a list of diseases to prioritise, participants tended to opt more frequently for lower scores. Therefore, we propose to replace the criterion of mortality by case fatality, as presented in Table 2, because mortality is implicitly dependant on incidence, whereas case fatality is another criterion for burden of disease complementing the criterion of severity. Among the selected diseases presented, the proposed exchange would somewhat lower the score for influenza but it does not seem to result in a relevant change of ranking.

A five-tiered scoring system as used in the overview of communicable diseases or in the Dubrovnik pledge could allow for a more differentiated scoring than the three-tiered system we used [2-4]. However, the challenge to generate clear definitions for each score increases with the number of scores. For many diseases and criteria information may not be available in the detail needed to permit such a differentiated approach.

The examples in Table 5 demonstrate that some diseases that were far apart in the unweighted scaling moved close together after weighting had been applied. This makes it obvious that weighting is important and that it may result in changes in both directions. There is reason to believe that the objectiveness of the procedure is increased if weighting is done independently of, and prior to,

Figure 2

Distribution of pathogens by total weighted and unweighted scores during prioritisation, Robert Koch Institute, 2008

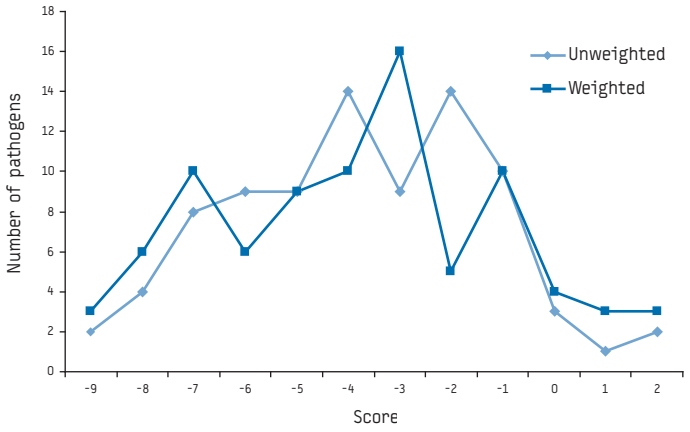


Table 5

Prioritisation scores for five selected pathogens out of 85, Robert Koch Institute, 2008

		Crude weighted scores				
		Maximum		Median		Minimum
Disease	Weight	Influenza	Rotavirus	Rubella	Cyclosporiasis	Cholera
Burden of disease						
Incidence	10.7	10.7	10.7	0	-10.7	-10.7
Severity	10.3	0	-10.3	-10.3	-10.3	0
Mortality	8.4	8.4	0	-8.4	-8.4	-8.4
Epidemiologic dynamic						
Outbreak potential	10.1	10.1	10.1	10.1	0	-10.1
Epidemiologic trend	7.7	0	0	0	0	-7.7
Emerging potential	5.4	-5.4	-5.4	-5.4	0	0
Information need						
Evidence for risk factors /groups	5.5	-5.5	-5.5	-5.5	5.5	-5.5
Validity of epidemiologic information	5.4	-5.4	-5.4	0	5.4	-5.4
Political agendas, public awareness	5.2	5.2	0	-5.2	-5.2	0
Evidence for pathogenesis	3.4	-3.4	-3.4	-3.4	0	-3.4
Health gain opportunity						
Preventability	8.0	8	-8	0	0	-8
Treatability	5.2	0	-5.2	5.2	0	-5.2
Total weighted score (crude)		22.7	-22.8	-22.9	-23.7	-64.4
Total unweighted score		1	-5	-4	-2	-9
Total weighted score (normalised to a scale from +2 to -9)		2	-4	-4	-4	-9

scoring. This is a way to avoid individual preferences of participants biasing the process. The advantage of quantitatively determining the weight for each individual criterion is that other institutions may choose to apply different weights to adapt the ranking to their respective mission. This increases the flexibility of the system and allows it to be used for different applications. For example the Eurostat task force on human health issues related to food safety has recently adopted a number of our criteria and also our concept of weighting in an attempt to identify the top 20 diseases from the inventory of food safety related diseases in Europe. (Ana Martinez, Eurostat, personal communication)

Call for comments

For an upcoming update of our prioritisation methodology we plan to include the views from experts from various fields and institutions outside the RKI.

While suggesting that a structured prioritisation approach similar to the one presented here is useful, there are still a number of questions that we plan to re-assess before going through such a procedure again:

- Does the list contain all relevant pathogens?
- Do the 12 criteria cover the relevant characteristics for prioritisation and are they not redundant or strongly dependant on each other? If other categories are missing, would the available information suffice to allow scoring based on defined scores?
- For which categories would a five-tiered scaling be a major improvement and if so would it be feasible to generate clear definitions for each scale?
- Are the existing definitions for the three scores for each criterion clear and plausible? Can they be applied? Are they valid to detect differences?
- Is the weighting of the criteria plausible?
- How large should the group of participating experts be and how should it be composed?

We invite suggestions, feedback and answers to the questions above through a structured web-based questionnaire available from http://www.rki.de/EN > Prevention of infection > Infectious Disease Surveillance > Pathogen prioritization. This may initiate a fruitful discussion in the scientific community and provide some guidance on how to improve our prioritisation scheme and maybe that of other institutions. Ultimately, we hope this will in return contribute to rational allocation of attention and resources in the control and prevention of infectious diseases.

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