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## Editorials



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# The city, its people, their health and tuberculosis

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City life appears destined to dominate the future of mankind in both the developed and developing world. If current trends persist into the coming decades, all population growth at global level will occur in towns and cities [1]. The number and size of big cities are set to increase. The proportion of the world's population living in cities is forecasted to go up from 52% in 2011 to 67% in 2050 [2]. In more developed regions, including much of the European Union (EU), close to 90% of the population is expected to become urbanised by 2050.

Economic pressures of different forms fuel these trends. For many people, however, the benefits of resettlement in cities and towns come at a price of greater risk to security and health through social exclusion. The rapid urbanisation that followed the Industrial Revolution led to a deterioration in public health in a number of western European cities. Homelessness, poverty, migration, overcrowding, and substance abuse are common in cities today and these risks often overlap in the same individuals, contributing to their descent into ill health. Tuberculosis (TB) tends to be barometric of this trend.

It has been known for a number of years that the risk of TB in many western European countries was higher for persons dwelling in a big city than those in rural areas; this was documented in a study of 20 cities in 11 European countries in 2003 [3]. However, the paper by De Vries et al. in this issue of *Eurosurveillance* presents a more recent roundup of European data from more cities and more countries [4]. It also reflects the realities of a more diverse EU, which has expanded eastwards since 2004 to encompass countries which generally had higher rates of TB than most of the EU15 countries before the enlargement. The data from this study thus allowed the authors to comment on observations which are better profiled than before. One of these is the inverse relationship between overall TB national case rates and the ratio of TB case rates in cities and towns compared with the rest of the country. This finding lends evidence to the widely held belief that as TB becomes rarer, the epidemic becomes more concentrated in place and population. It is also noteworthy that most cities with a rate ratio larger than 2.0 had a population of less than 1 million. The finding that TB presents a challenge beyond just the capital cities, including settlements which do not come anywhere close to mega-cities, is important. It clearly has implications for the allocation of resources for TB control within a country's borders. The authors also comment on time trends in population rates of TB in some of the bigger cities: this is a challenging exercise given that year-on-year fluxes may not be accurately captured in the population estimates of large conurbations, particularly among mobile individuals expected to be at greatest risk of TB, such as the homeless and recent migrants. Nonetheless, any over-estimation in rates due to inexact statistics is unlikely to invalidate the conclusions drawn on the broad overall patterns observed in the last two decades. Otherwise, just as the TB notification rates in a country mask important disparities in risk of infection and disease within a country, the frequency of TB in a city is not expected to be homogenously distributed within its precincts. The application of geographic information system (GIS) techniques such as the heat maps illustrated in the article by De Vries et al., are useful to describe the spatial distribution of TB disease within a city and can be helpful for field epidemiology and for the matching of investment with existing need. For European countries to achieve TB elimination (less than one TB case per million population per year) [5], they will need to rope in information technology methods such as these to locate individuals at risk of disease, to ensure that TB (including its drug-resistant forms) is detected early and fast, and to ensure reliable delivery of treatment.

A number of these innovations are put forward as solutions in a second article on this subject in this issue of *Eurosurveillance* [6], which proposes a multi-pronged action framework for TB prevention and care in the bigger cities of the EU. This welcome development is the end product of efforts by leading TB experts and technical partners which snowballed steadily over the last decade. The consensus achieved in this respect implies more statements than one.

Firstly, it represents a high-level recognition of the crucial position that urbanisation occupies and will continue to have among the different focused approaches to TB control. Secondly, it grounds its proposals for the way forward in the most recent knowledge and best

available information on TB epidemiology in Europe and elsewhere, with the authors identifying critical points for priority action. Thirdly, it is pragmatic in nesting these recommendations within initiatives which are already in place and seeks opportunities to actively improve impact, such as targeting at-risk individuals at any health service encounter. This is crucial given that the clients often belong to hard-to-reach population groups. Fourthly, the approach shows innovation in attempting to harness factors which lie outside the traditional territory of the TB practitioner, including the social factors, educational measures and legal dimensions through a conceptual model of 'structural and intermediary determinants'. One inadvertent victim of this approach, however, appears to be the domain of drug-resistant TB, which is mentioned in the context of infection control but afforded little focus in other respects, such as early diagnosis and effective treatment. The circumstances of TB patients in an urban setting may predispose to the propagation of drug-resistance as a result of inadequate case holding while on treatment and the higher population density; moreover the EU includes some countries with very high levels of multidrug resistance among TB cases.

Finally, another aspect of the paper by van Hest et al. worth highlighting is that evidence and recommendations were rated according to the Scottish Intercollegiate Guidelines Network (SIGN; www.sign.ac.uk), a system which takes into account considerations other than quality of evidence when formulating recommendations but differs from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method used by the World Health Organization and others (www.gradeworkinggroup.org). It is important to note in this context that, as in many other fields of TB care, none of the evidence on which this consensus statement was based came directly out of randomised controlled trials (which at times are impossible or inappropriate to answer questions which are relevant to this topic) and nearly all of it would be judged to be of low or very low quality by the GRADE method.

In conclusion, these two complementary papers represent an important addition to the TB bibliography of Europe and beyond. Public health specialists and decision makers at municipal as well as national levels should find the conclusions and directions of particular value. The timing of these publications is also apposite given that it comes a couple of weeks ahead of World TB Day on 24 March [7], which this year is focused on the three million TB patients estimated to be missed annually by the national health systems in the world because of under-reporting or lack of access to reliable diagnosis [8].

## Conflict of interest

None declared.

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# Zika virus infection complicated by Guillain-Barré syndrome – case report, French Polynesia, December 2013

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**Zika fever, considered as an emerging disease of arboviral origin, because of its expanding geographic area, is known as a benign infection usually presenting as an influenza-like illness with cutaneous rash. So far, Zika virus infection has never led to hospitalisation. We describe the first case of Guillain–Barré syndrome (GBS) occurring immediately after a Zika virus infection, during the current Zika and type 1 and 3 dengue fever co-epidemics in French Polynesia.**

We report on a French Polynesian patient presenting a Zika virus (ZIKA) infection complicated by Guillain–Barré syndrome (GBS).

## Clinical description

In November 2013, a Polynesian woman in her early 40s, with no past medical history with the exception of acute articular rheumatism, was hospitalised in our institution for neurological deficits. She had been evaluated one day before (Day 0: onset of neurological disorders) at the emergency department for paraesthesia of the four limb extremities and discharged. At Day 1, she was admitted to the department of neurology through the emergency department because paraesthesia had evolved into ascendant muscular weakness suggestive of GBS. At Day 3, she developed a tetraparesis predominant in the lower limbs, with paraesthesia of the extremities, diffuse myalgia, and a bilateral but asymmetric peripheral facial palsy. Deep tendon reflexes were abolished. There was no respiratory nor deglutition disorders. The patient developed chest pain related to a sustained ventricular tachycardia, and orthostatic hypotension, both suggestive of dysautonomia. The echocardiography was normal, without signs of pericarditis or myocarditis. The electromyogram confirmed a diffuse demyelinating disorder, with elevated distal motor latency, elongated F-wave, conduction block and acute denervation, without axonal abnormalities. The administration of intravenous polyvalent immunoglobulin (0.4 g/kg/day for 5 days) allowed a favourable evolution, with no respiratory impairment necessitating tracheotomy or intensive care unit monitoring, and the patient was discharged home at Day 13. Paraparesis persisted after the end of hospitalisation, that imposed the use of a walking frame, and the facial palsy slowly disappeared. At Day 40, she was able to walk without help and had a satisfying muscular strength score of 85/100.

Retrospectively, anamnestic data revealed that she had suffered from an influenza-like syndrome at Day – 7, with myalgia, febricula, cutaneous rash, and conjunctivitis. Because an epidemic of Zika fever, which is still ongoing [1], had begun a few weeks prior to the patient presenting this syndrome, Zika fever was suspected.

## Laboratory analysis

Laboratory findings showed no inflammatory syndrome and the blood count was normal. A twofold increase in transaminase level was observed. The analysis of cerebrospinal fluid (CSF) disclosed an albuminocytological dissociation with 1.66 g/L proteins (norm: 0.28–0.52) and 7 white cells/mL (norm<10). Glycorrhachia was normal at 0.60 g/L. Usual aetiologies of GBS were eliminated: serological tests for human immunodeficiency virus (HIV), hepatitis B and *C, Campylobacter jejuni* and *Leptospira* were negative; and serological tests for cytomegalovirus, Epstein–Barr virus, and herpes simplex virus type 1 and 2 concluded to resolute infections.

Direct detection of dengue virus (DENV) by non-structural protein 1 (NS1) antigen (SD Bioline Dengue NS1 Ag

ELISA, ALERE Australia) and reverse transcription-polymerase chain reaction (RT-PCR) [2], and ZIKA by RT-PCR [3], were negative on blood samples eight days after the beginning of influenza-like symptoms (corresponding to Day 1), prior to the administration of intravenous immunoglobulin. Blood samples taken at eight and 28 days after the beginning of the influenza-like syndrome were both positive for ZIKA-specific IgM and ZIKA- and DENV-specific IgG, assessed by in-house enzyme-linked immunosorbent assays (in-house IgM antibody capture (MAC)- enzyme-linked immunosorbent assay (ELISA) and indirect IgG ELISA using inactivated antigen). On the last serum specimen sampled 28 days after the onset of influenza like syndrome, antibody specificity was determined by plaque reduction neutralisation test (PRNT) against serotype 1 to 4 DENV (DENV1–4) and ZIKA. A 90% neutralisation titre ›1/320 for DENV1, 1/80 for DENV2, ›1/320 for DENV3, 1/20 for DENV4 and ›1/320 for ZIKA confirmed that neutralising antibodies against ZIKA and the four DENV serotypes were present in the sera of the patient. These serological analyses indicated a recent infection by ZIKA, and argued for resolute infections by DENV1–4.

## Background on Zika virus infections

Discovered in 1947 in the Zika forest in Uganda, ZIKA is an arbovirus of the flavivirus genus belonging to the *flaviviridae* family, as dengue, yellow fever, Japanese encephalitis, West Nile, and Saint-Louis encephalitis viruses. First human cases of ZIKA infection were described in the 1960s, first in Africa, then in south-east Asia [4-6]. Until 2007 when a large epidemic was described in Yap (Micronesia) [7], ZIKA infections remained limited to sporadic cases or small-scale epidemics. During the epidemic in Yap, three quarters of the local population are estimated to have been infected [7]. The expanding distribution area of ZIKA makes Zika fever an emerging disease [8], confirmed by the present epidemic affecting French Polynesia since October 2013, and the New Caledonian reported cases since the end of 2013 [1].

The real incidence of Zika fever is unknown, due to clinical manifestations mimicking dengue virus infection, and to lack of simple reliable laboratory diagnostic tests. In endemic areas, epidemiological studies showed a high prevalence of antibodies against ZIKA [9,10]. For instance, Yap's epidemic in 2007 resulted in an attack rate of 14.6/1,000 inhabitants and a seroprevalence of 75% after the epidemic. However, this prevalence is certainly overestimated, due to cross-reaction between antibodies directed against ZIKA and other arboviruses such as DENV [3,11].

Like other arboviral diseases, ZIKA is transmitted by arthropods, mainly involving vectors of the *Aedes* genus, as ZIKA was isolated from numerous species of *Aedes* mosquitoes in different parts of the world [12-14]. Interestingly, since the first description of *Ae. albopictus* as a potential vector of ZIKA in 2007 by Wong et al., other reports have suggested that the rapid worldwide expansion of this vector could be responsible for the emergence of new ZIKA infection epidemics, including in urban areas [15,16]. Based on epidemiological evidence, *Ae. aegypti* and *Ae. polynesiensis* are suspected to be the vectors for the ongoing French Polynesia's epidemic (data not shown). The abundance of competent vectors in the Pacific areas and air travel of viraemic individuals between Pacific island countries and territories are very likely to account for the expansion of ZIKA in this part of the world.

Infection is reported to be symptomatic in 18% of cases only [7]. When symptomatic, ZIKA infection usually presents as an influenza-like syndrome, often mistaken with other arboviral infections like dengue or chikungunya. The typical form of the disease associates a low-grade fever (between 37.8°C and 38.5°C), arthralgia, notably of small joints of hands and feet, with possible swollen joints, myalgia, headache, retroocular headaches, conjunctivitis, and cutaneous maculopapular rash. Digestive troubles (abdominal pain, diarrhoea, constipation), mucous membrane ulcerations (aphthae), and pruritus can be more rarely observed. A post-infection asthenia seems to be frequent [5,7,17].

Confirmed diagnosis is given by RT-PCR, which specifically detects the virus during viraemia [3]. In-house ELISA serological tests can testify the presence of ZIKA IgM and flaviviruses IgG, whereby specificity is determined by seroneutralisation.

## Discussion and conclusion

During this ongoing Zika fever outbreak in French Polynesia, we report the first case of GBS developing seven days after an influenza-like illness evoking ZIKA infection. Based on IgM/IgG serological results and PNRT which, according to our experience, is reliable and specific enough to differentiate a recent ZIKA infection from cross-reactions due to former infections to DENV, we believe that this is the first case of hospitalisation because of a severe ZIKA infection.

Since the beginning of this epidemic, and as up to 8,200 cases of ZIKA infection have already been reported of a 268,000 total population, the incidence of GBS has been multiplied by 20 in French Polynesia (data not shown), raising the assumption of a potential implication of ZIKA.

Underlying physiopathological mechanisms of Zika-related GBS is unknown, and could be of immunological origin as described with other infectious agents [18]. There is also no explanation for the emergence of this previously undescribed complication, which could lie in a genetic evolution of the virus to a more pathogenic genotype, or a particular susceptibility in the Polynesian population.

As suggested by DENV and ZIKA serological tests in our patient, the simultaneous epidemics of type 1 and 3 dengue fever may also be a predisposing factor

for developing GBS during Zika fever, as DENV infection had also been associated with GBS [19,20]. Our patient, like part of others who also presented a GBS, harboured serological markers of resolute dengue and recent ZIKA infections. This raises the hypothesis of a sequential arboviral immune stimulation responsible for such unusual clustering of GBS cases during concurrent circulation of ZIKA and two dengue serotypes. The risk of developing GBS would be consequently underlain by a specific sequence of DENV and ZIKA infections.

Therefore in endemic areas, clinician should be aware of the risk of diffuse demyelinating disorder in case of ZIKA infection.

## Conflict of interest

None declared.

## Authors' contributions

EO, LW, FV wrote the manuscript. EO, LW, PL, FG took part in the clinical management of the patient. SL, DM collaborated in molecular biology techniques. ILG collaborated on the virological investigation and on the manuscript writing. All authors participated in the outbreak investigation. All authors read and approved the final manuscript.

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# Influenza vaccine effectiveness in Spain 2013/14: subtype-specific early estimates using the cycEVA study

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**Adjusted early estimates of the 2013/14 influenza vaccine effectiveness (VE) in Spain for all age groups was 35% (95% CI: −9 to 62), 33% (95% CI: −33 to 67) and 28% (95% CI: −33 to 61) against any influenza virus type, A(H1N1)pdm09 and A(H3N2) viruses, respectively. For the population targeted for vaccination, the adjusted VE was 44% (95% CI: −11 to 72), 36% (95% CI: −64 to 75) and 42% (95% CI: −29 to 74), respectively. These preliminary results in Spain suggest a suboptimal protective effect of the vaccine against circulating influenza viruses.**

## Early assessment of influenza vaccine effectiveness in Spain at national level

In the current influenza season, Spain has experienced a relatively early influenza epidemic compared with other European countries [1]. We present here nationwide early estimates of the effectiveness of the 2013/14 seasonal trivalent influenza vaccine in Spain in preventing medically attended laboratory-confirmed influenza-like illness (ILI) infections, by virus type and subtype in all age groups and in the population targeted for vaccination, during the time when the influenza epidemic in Spain was increasing (9 December 2013 to 26 January 2014). Our early estimates suggest a suboptimal protective effect of the vaccine in preventing medically attended A(H1N1)pdm09 and A(H3N2) laboratory-confirmed influenza.

## Background

Since 2008, Spain has been providing interim influenza vaccine effectiveness (VE) results using the cycEVA study – casos y controles para la Efectividad de la Vacuna Antigripal [cases and controls for monitoring influenza vaccine effectiveness], the Spanish component of the I-MOVE (Monitoring Vaccine Effectiveness in Europe) network [2,3]. The agreement between interim and final influenza VE estimates supports the use of interim assessments as a proxy for final VE results [4,5].

In February 2013, the Vaccine Strain Selection Committee of the World Health Organization (WHO) formally received for the first time a compilation of preliminary influenza VE estimates for the 2012/13 season from Europe, Canada and the United States (US) [6]. Interim estimates 2013/14 and final 2013 estimates of influenza VE from countries in the northern and southern hemisphere, respectively, together with results of the characterisation of influenza viruses and vaccine serological studies, have contributed again this year to the decision of the Committee in February on the recommended composition of influenza vaccines for the forthcoming (2014/15) northern hemisphere influenza season [7]. Interim 2013/14 VE estimates have shown substantial protection against laboratory-confirmed A(H1N1)pdm09 illness in Canada and US [8,9] but suboptimal protection against this subtype in the Spanish Navarre region [10].

The results presented here at national level – the first at national level in Europe, in a scenario of multiple Spanish regions with probable differences in some epidemiological features or circulating viruses – might

**Table 1**

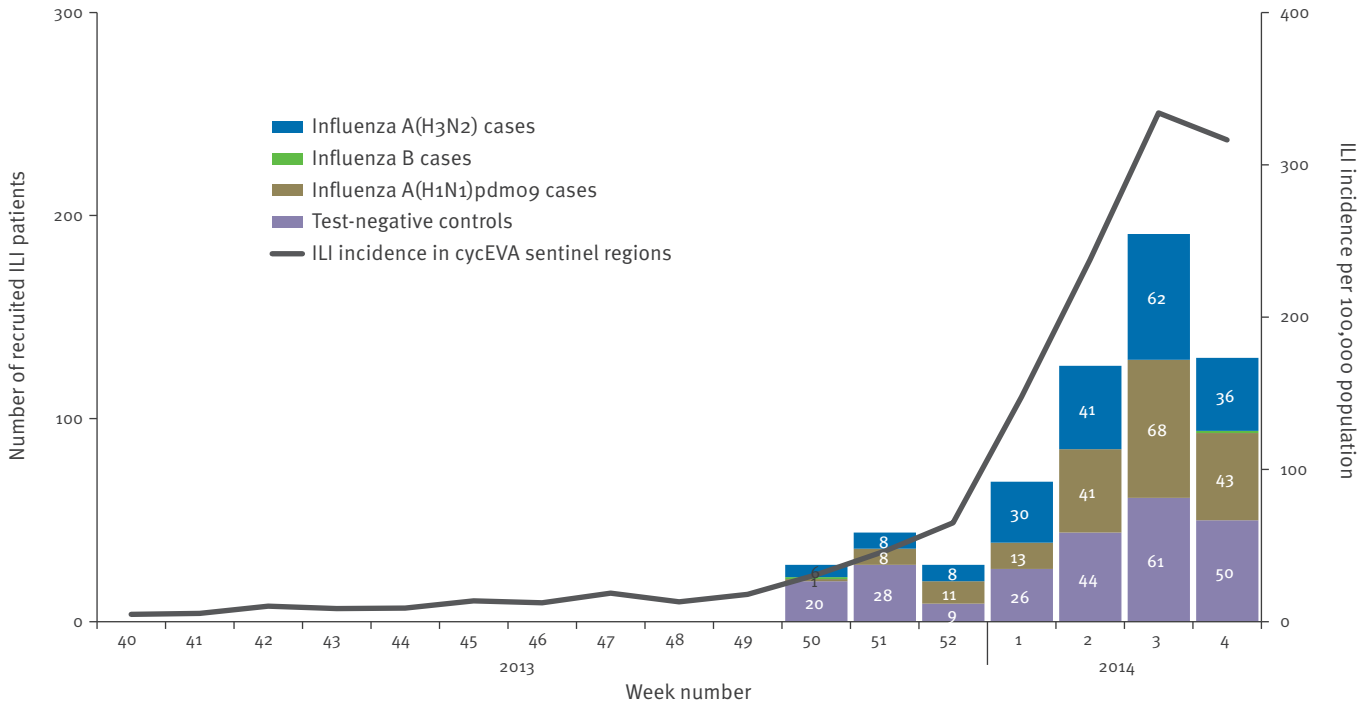
Reference haemagglutinin sequences obtained from the EpiFlu database of the Global Initiative on Sharing Avian Influenza Data (GISAID) and used in phylogenetic analysis, Spanish Influenza Surveillance System, week 40 2013–week 4 2014 (30 September 2013–26 January 2014)

| Segment ID | Segment | Country | Collection date | Isolate name | Originating laboratory | Submitting laboratory | Authors |
|---|---|---|---|---|---|---|---|
| EPI353304 | HA | Australia | 2007-02-06 | A/Brisbane/10/2007 | Queensland Health Scientific Services | WHO Collaborating Centre for Reference and Research on Influenza | Iannello, P; Komadina, N |
| EPI182941 | HA | Australia | 2009-04-07 | A/Perth/16/2009 | Pathwest QE II Medical Centre | WHO Collaborating Centre for Reference and Research on Influenza | Deng, Y-M; Iannello, P; Erneste, J; Komadina, N |
| EPI272062 | HA | Australia | 2009-06-02 | A/Victoria/208/2009 | Victorian Infectious Diseases Reference Laboratory | WHO Collaborating Centre for Reference and Research on Influenza | Deng, Y-M; Iannello, P; Caldwell, N; Leang, S-K; Komadina, N |
| EPI335923 | HA | United States | 2010-12-30 | A/Iowa/19/2010 | Iowa State Hygienic Laboratory | Centers for Disease Control and Prevention | Garten, R |
| EPI279881 | HA | Hong Kong (SAR) | 2010-07-05 | A/Hong Kong/2121/2010 | Government Virus Unit | National Institute for Medical Research | Gregory, V |
| EPI278805 | HA | United States | 2010-07-13 | A/Alabama/05/2010 | U.S. Air Force School of Aerospace Medicine | Centers for Disease Control and Prevention | Garten, R |
| EPI318272 | HA | Sweden | 2011-02-21 | A/Stockholm/18/2011 | Swedish Institute for Infectious Disease Control | Swedish Institute for Infectious Disease Control | Brytting, M |
| EPI358885 | HA | Greece | 2012-02-01 | A/Athens/112/2012 | Hellenic Pasteur Institute | National Institute for Medical Research | Gregory, V |
| EPI450687 | HA | Madagascar | 2012-06-01 | A/Mahajanga/3628/2012 | Institut Pasteur de Madagascar | National Institute for Medical Research | Gregory, V |
| EPI466963 | HA | Madagascar | 2013-02-25 | A/Maevatanana/563/2013 | Institut Pasteur de Madagascar | National Institute for Medical Research | Gregory, V |
| EPI335697 | HA | Slovenia | 2011-01-25 | A/Slovenia/537/2011 | Laboratory for Virology, National Institute of Public Health | National Institute for Medical Research | Gregory, V |
| EPI349103 | HA | Australia | 2011-10-24 | A/Victoria/361/2011 | Melbourne Pathology | WHO Collaborating Centre for Reference and Research on Influenza | Deng, Y-M; Caldwell, N; Iannello, P; Komadina, N |
| EPI377499 | HA | United States | 2012-04-15 | A/Texas/50/2012 | Texas Department of State Health Services-Laboratory Services | Centers for Disease Control and Prevention | Garten, R |
| EPI360950 | HA | Germany | 2011-07-03 | A/Berlin/93/2011 | National Institute for Medical Research | Centers for Disease Control and Prevention | Garten, R |
| EPI397362 | HA | United States | 2012-07-09 | A/Hawaii/22/2012 | State of Hawaii Department of Health | Centers for Disease Control and Prevention | Garten, R |
| EPI467994 | HA | Ireland | 2013-04-02 | A/Ireland/M28390/2013 | National Virus Reference Laboratory of Ireland | National Institute for Medical Research | Gregory, V |
| EPI460558 | HA | Russian Federation | 2013-03-12 | A/Samara/73/2013 | WHO National Influenza Centre | National Institute for Medical Research | Gregory, V |

We gratefully acknowledge the authors, originating and submitting laboratories of the sequences, other than those coming from our surveillance network, retrieved from GISAID's EpiFlu database.

**Figure 1**

Recruited influenza cases (n=445) and test-negative controls (n=229) and influenza-like illness incidence in sentinel regions, cycEVA study, Spain, week 50 2013–week 4 2014 (9 December 2013–26 January 2014)




cycEVA: casos y controles para la Efectividad de la Vacuna Antigripal [cases and controls for monitoring influenza vaccine effectiveness]; ILI: influenza-like illness.

add substantial value to the previous estimates from Navarre regarding the suboptimal protective effect of the vaccine. By sharing these results with the scientific community, we are providing evidence that will help to fill the current gaps in knowledge of the relationship between antigenic match and the reported effectiveness of the vaccine.

## Estimating vaccine effectiveness and determining virus type

In the 2013/14 influenza season, six of the 17 regional networks belonging to the Spanish Influenza Sentinel Surveillance System participated in the cycEVA study. The methods used were similar to those carried out in previous seasons in the cycEVA study [11].

Influenza cases were ILI patients who tested positive for influenza virus using real-time reverse-transcription polymerase chain reaction or virus culture. Controls were ILI patients with swabs testing negative for any type of influenza virus.

The WHO National Influenza Centre in Madrid selected a subset of influenza isolates from the entire sentinel surveillance system for genetic characterisation by sequencing the amplified HA1 fragment of the viral haemagglutinin gene. Isolates were selected in order to be as representative as possible of viruses circulating in all Spanish regions. Thus they included viruses collected in every phase of the influenza season (beginning, epidemic peak and end of the season). They were also selected to include all ages, irrespective of the vaccination status of the patients. Phylogenetic analysis and molecular evolutionary analyses of the HA1 sequences was conducted using MEGA version 5 [12] in order to characterise the influenza A strains. Reference haemagglutinin nucleotide sequences were obtained from the Global Initiative on Sharing Avian Influenza Data (GISAID) [13] (Table 1).

We used logistic regression to calculate influenza VE from week 50 (starting 9 December) 2013 to week 4 (starting 26 January) 2014, including in the model potential confounding factors and restricting the analysis to those swabbed within seven days of symptom onset. In a sensitivity analysis, we calculated influenza VE in the population targeted for vaccination (individuals over six months-old with chronic conditions, people with risk factors (pregnancy, in women aged 15–44 years, or morbid obesity (body mass index ≥40 kg/m$^2$), people aged over 59 years (over 64 years in some regions), healthcare workers and caregivers).

**Table 2**

Characteristics of laboratory-confirmed cases with influenza A(H1N1)pdm09 or A(H3N2) viruses and test-negative controls, cycEVA study, Spain, week 50 2013–week 4 2014 (9 December 2013–26 January 2014) (n=601)

| Variables | Test-negative controls, n=229[a] | Influenza A(H1N1)pdm09 cases, n=184[a] | P value[b,c] | Influenza A(H3N2) cases n=188[a] | P value[c,d] |
|---|---|---|---|---|---|
| | Number/total number (%)[e] | Number/ total number (%)[e] | | Number/ total number (%)[e] | |
| Age group in years | | | | | |
| 0–4 | 22/229 (9.6) | 7/184 (3.8) | 0.005 | 13/188 (6.9) | 0.617 |
| 5–14 | 30/229 (13.1) | 30/184 (16.3) | | 20/188 (10.6) | |
| 15–64 | 153/229 (66.8) | 140/184 (76.1) | | 135/188 (71.8) | |
| ≥65 | 24/229 (10.5) | 7/184 (3.8) | | 20/188 (10.6) | |
| Median age in years (range) | 36 (0–92) | 37 (1–80) | 0.868[f] | 37 (0–89) | 0.778[e] |
| Male | 121/229 (52.8) | 102/184 (55.4) | 0.599 | 94/188 (50.0) | 0.564 |
| Any chronic condition reported | 50/228 (21.9) | 32/184 (17.4) | 0.251 | 47/187 (25.1) | 0.443 |
| Any risk factor reported[g] | 6/211 (2.8) | 5/184 (2.7) | 0.947 | 5/165 (3.0) | 0.915 |
| Any hospitalisation for chronic conditions in previous year | 0/229 (0) | 3/184 (1.6) | 0.052 | 0/188 (0) | 0.100 |
| Median number of visits to a GP or pediatrician in previous year per patient (range) | 3 (0–44) | 3 (0–36) | 0.450[f] | 3 (0–27) | 0.775[f] |
| Smoker | 38/227 (16.7) | 23/184 (12.5) | 0.229 | 24/186 (12.9) | 0.277 |
| Interval between symptom onset and swabbing less than 4 days | 223/229 (97.4) | 178/184 (96.7) | 0.700 | 184/188 (97.9) | 0.744 |
| Population targeted for vaccination | 78/218 (35.8) | 43/184 (23.4) | 0.027 | 66/172 (38.4) | 0.598 |
| Vaccination status | | | | | |
| All ages | | | | | |
| Received seasonal 2013/14 vaccine[h] | 38/229 (16.6) | 21/184 (11.4) | 0.085 | 30/188 (16.0) | 0.681 |
| Received both seasonal 2013/14 and 2012/13 vaccines | 35/229 (15.3) | 20/184 (10.9) | 0.278 | 28/188 (14.9) | 0.623 |
| Targeted for vaccination | | | | | |
| Received seasonal 2013/14 vaccine[h] | 28/78 (35.9) | 12/43 (27.9) | 0.371 | 17/66 (25.8) | 0.191 |
| Received both seasonal 2013/14 and 2012/13 vaccines | 24/78 (30.8) | 11/43 (25.6) | 0.760 | 16/66 (24.2) | 0.424 |

GP: general practitioner; ILI: influenza-like illness.

[a] Cases and controls recruited during the specified time period and with an interval between ILI symptom onset and swabbing of less than eight days.

[b] P value for A(H1N1)pdm09 cases versus controls.

[c] Chi-squared test or Fisher's exact test.

[d] P value for A(H3N2) cases versus controls.

[e] Unless otherwise indicated. The denominator changes for variables in which the information was missing for some patients.

[f] Non-parametric test of the median.

[g] Defined as pregnancy (in women aged 15–44 years) and/or morbid obesity (body mass index ≥40 kg/m$^2$).

[h] Vaccination at least 14 days before the onset of influenza like illness symptoms.

## Early national vaccine effectiveness estimates

### Description of the 2013/14 influenza season in Spain

The 2013/14 influenza season in Spain started in week 1 (30 December 2013–5 January 2014) and reached the epidemic peak in week 4 (20–26 January 2014) at both the national level and in the six regions participating in the cycEVA study [14]. It was a medium-intensity influenza season, clearly dominated by mixed circulation of influenza A viruses: 61% (571/929) A(H1N1) pdm09 and 39% (358/929) A(H3N2) influenza [14].

### Participants' characteristics

Among the 217 participating sentinel physicians in the study, 167 (77%) recruited at least one ILI patient. Of the 687 ILI patients recruited, 202 (29%) belonged to the population targeted for influenza vaccination. After excluding 15 patients swabbed more than seven days

**Table 3**

Crude and adjusted seasonal vaccine effectiveness estimates against laboratory-confirmed influenza by virus type/subtype, overall and among the target population for influenza vaccination, cycEVA study, Spain, week 50 2013–week 4 2014 (9 December 2013–26 January 2014)

| Population included | All influenza viruses | Influenza A(H1N1)pdm09 | Influenza A(H3N2) |
|---|---|---|---|
| All patients | | | |
| Number of patients for the analysis: cases + controls | 674 | 413 | 417 |
| Number of cases/controls | 445/229 | 184/229 | 188/229 |
| Number of vaccinated cases/vaccinated controls | 53/38 | 21/38 | 30/38 |
| Crude VE % (95% CI) | 32 (–7 to 56) | 35 (–15 to 63) | 5 (–61 to 43) |
| Adjusted VE[a] %(95% CI) | 35 (–9 to 62) | 33 (–33 to 67) | 28 (–33 to 61) |
| Population targeted for vaccination | | | |
| Number of patients for the analysis: cases + controls | 299 | 121 | 144 |
| Number of cases/controls | 121/78 | 43/78 | 66/78 |
| Number of vaccinated cases/vaccinated controls | 30/27 | 12/27 | 17/27 |
| Crude VE % (95% CI) | 38 (–16 to 67) | 27 (–65 to 98) | 34 (–35 to 68) |
| Adjusted VE[a] % (95% CI) | 44 (–11 to 72) | 36 (–64 to 75) | 42 (–29 to 74) |

CI: confidence interval; VE: vaccine effectiveness.

[a] Adjusted for age (age groups adjusted for: 0–4, 5–14, 15–64 and ≥65 years), sex, severity, number of general practitioner visits, smoking history (had ever smoked), chronic conditions, pregnancy (in women aged 15–44 years), morbid obesity (body mass index ≥40 kg/m²) and week of swabbing.

after symptom onset, 674 ILI patients were included in the study, comprising 445 influenza cases – 188 with influenza A(H3N2) virus, 184 A(H1N1)pdm09, 71 influenza A not subtyped and two with influenza B virus– and 229 test-negative controls (Figure 1).

The percentage of the population targeted for vaccination was higher in the controls (35.8%, 78/218,) than in the A(H1N1)pdm09 cases (23.4%, 43/184) (Table 2). Vaccine coverage with the 2013/14 influenza vaccine was not statistically different among controls and A(H1N1)pdm09 or A(H3N2) cases, in all age groups and among the population targeted for vaccination. The majority of cases (96.7–97.9%, 178/184–184/188) and controls (97.4%, 223/229) were swabbed less than four days after symptom onset.

Of the 89 people vaccinated, there were 54 vaccine failures: 30 were positive for influenza A(H3N2) virus, 21 for influenza A(H1N1)pdm09 virus and three with an unknown influenza virus. Of the 54 vaccine failures, 30 were cases belonging to the target population for vaccination.

## Vaccine effectiveness estimates

The adjusted influenza VE for all age groups was 35% (95% CI: –9 to 62), 33% (95% CI: –33 to 67) and 28% (95% CI: –33 to 61) against any influenza virus type, A(H1N1)pdm09 and A(H3N2) viruses, respectively (Table 3).

Among the population targeted for vaccination, the adjusted influenza VE against any influenza virus type, A(H1N1)pdm09 and A(H3N2) viruses was 44% (95% CI: –11 to 72), 36% (95% CI: –64 to 75) and 42% (95% CI: –29 to 74), respectively (Table 3).

## Genetic analysis of selected isolates

Sequence analysis of the amplified HA1 genome fragments showed that all 93 influenza A(H1N1)pdm09 viruses studied clustered into the group 6B [15] represented by A/Norway/2417/2013 and defined by D97N, K163Q, S185T, S203T, A256T and K283E amino acid mutations compared with the vaccine virus A/California/07/2009.

Regarding influenza A(H3N2) virus, all 61 viruses studied clustered into the group 3C [15] which includes the A/Texas/50/2012 vaccine virus strain, but harboured some amino acid changes that make it possible to differentiate them into two subsets (named 3C.2 and 3C.3) (representative isolates are shown in Figure 2, including viruses collected in past seasons for a better understand the genetic drift of influenza A viruses). Six of the 61 viruses clustered within subgroup 3C.2 represented by A/Ireland/M28390/2013, defined by the HA1 amino acid substitution N128T. The remaining 55/61 viruses (90%) clustered within the subgroup 3C.3 represented by A/Samara/73/2013 and defined by N128A and R142G amino acid substitutions. Interestingly, we could differentiate 23 viruses within the 3C.3 subgroup with an additional L157S change, most of them (20 of 23) harbouring a second N122D mutation. Another subset of six viruses harbouring the K160R amino acid substitution could be identified within the 3C.3 subgroup. Changes in influenza A(H3N2) viruses were referred to the A/Texas/50/2012 vaccine virus strain.

## Figure 2

Phylogenetic tree showing genetic differences in HA1 fragment of the haemagglutinin of influenza A(H3N2) circulating viruses, Spanish Influenza Surveillance System, Spain, week 40 2013–week 4 2014 (30 September 2013–26 January 2014)


Phylogenetic relationships were inferred using the MEGA5 programme applying the neighbor-joining method and the Kimura 2-parameter model [12]. Representative isolates are shown, including viruses collected in past seasons to illustrate genetic drift. Viruses in bold are representative of groups 3C.1, 3C.2 and 3C.3, according to the European Centre for Disease Prevention and Control's *Influenza virus characterisation* [15].

## Discussion

Our interim point estimate in preventing A(H1N1) pdm09 infections was 33% in a 2013/14 season with circulating A(H1N1)pdm09 strains antigenically similar and genetically well conserved at the European level, as of week 4/2014 [15,16]. Suboptimal protective effects against well-conserved A(H1N1)pdm09 virus were previously described in Europe during the 2011/12 season by the I-MOVE network [17]. In Spain, during the 2010/11 season, early VE estimates against well-matched A(H1N1)pdm09 virus were also found to be lower than 50% (49%; 95% CI: 3 to 73) [2], which were highly consistent with the final estimates, 46% (95% CI: 0 to 72) [18]. Estimates recently published by Canada and the US for the 2013/14 season [8,9] against A(H1N1)pdm09 were higher than our results. A higher protective effect of the vaccine against A(H1N1) pdm09 in North America compared with Spain could be due to different characteristics of the circulating A(H1N1)pdm09 viruses: most of the viruses analysed were shown to be antigenically similar to the vaccine strain in Canada and the US. In Spain, antigenic tests for A(H1N1)pdm09 virus are unfortunately not yet available. In addition, in light of the positive effect of previous influenza vaccination described in Canada [19] and Spain [18], a higher proportion of the population previously vaccinated with the 2009 monovalent pandemic vaccine in Canada (about 40%) [8] compared with that in Spain (<10%) [18,20] could partly explain the higher VE estimates observed in Canada. The use of different types of influenza vaccine could also contribute to the differences between the results of both studies. However, our results were in line (VE below 50%) with those recently published by the Navarre region [10], a Spanish region that also participates in the cycEVA study and I-MOVE network. In the Navarre study, patients recruited in primary healthcare and in hospitals were included, giving similarly low influenza VE estimates in both settings. These observations were in accordance with the evolution of the influenza epidemic in Spain this season: a considerably higher number of severe hospitalised laboratory-confirmed cases were seen than in the two previous seasons. Of these cases, 40% had received the seasonal influenza vaccine [13]. The reasons behind these highly variable estimates of VE are still unclear.

Subtype-specific estimates of VE for influenza A(H3N2) were also in the lower range of VE points described in previous seasons (range: 25–60% [11,21-23]), with adjusted estimates of 28% and 42% for all age groups and population targeted for vaccination, respectively. Reduced protection from influenza A(H3) infection has been described in previous seasons worldwide, including in Spain and the rest of Europe during the 2011/12 season, when A(H3) last circulated as the predominant virus, but was poorly matched to the vaccine [11,23]. The importance of the amino acid changes we describe in the circulating A(H3N2) virus in Spain will be studied at the end of the season once the haemagglutination inhibition assays have been carried out. However, it is important to highlight that the L157S and N122D mutations identified are located in the HA1 antigenic sites B and A, respectively, of A(H3N2) viruses: this could indicate a suboptimal protective effect of the current vaccine against A(H3N2) virus in Spain.

For the 2014/15 northern hemisphere influenza season, WHO has recommended the inclusion of the same strains included in the current seasonal influenza vaccine [24]. Final estimates in Spain with a larger sample size will allow us to confirm the extent of the protective value of the 2013/14 influenza vaccine in Spain and could give an indication of what could be expected in other countries in the northern hemisphere

Although VE estimates are subject to change over time, some studies have demonstrated agreement between interim and final influenza VE estimates, with early estimates within five to seven percentage points of final estimates [5,22]. Using the cycEVA study, the early [2,3] and final estimates [11,18] of the influenza VE in the 2010/11 and 2011/12 seasons in Spain have been similar.

The main limitation of our study was the sample size, which makes estimates for virus subtypes imprecise; therefore, final estimates should be obtained at the end of the influenza season.

Early estimates of influenza VE can help to guide health authorities in influenza prevention and provide useful information for the WHO strain selection process. Future influenza VE studies worldwide are necessary to gain more knowledge about which virus amino acid changes could be influencing the protective effect of the current influenza vaccines. Although our results indicate the protection against A(H1N1)pdm09 and A(H3N2) viruses was suboptimal, the VE was higher among those at risk of severe influenza complications, underlying the importance of annual influenza vaccination. The suboptimal protective effect of the vaccine should also lead to a clear public health message underlying the importance of early antiviral treatment for patients at high risk of influenza complications, and the adoption of non-pharmacological preventive measures to avoid influenza infection.

## Members of the Spanish Influenza Sentinel Surveillance System (SISS)

Physicians of the influenza sentinel surveillance networks of: Andalucía, Aragón, Asturias, Baleares, Canarias, Cantabria, Castilla La Mancha, Castilla y León, Cataluña, Comunitat Valenciana, Extremadura, Madrid, Navarra, País Vasco, La Rioja, Ceuta and Melilla.

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## Conflict of interest

None declared.

## Authors' contributions

Silvia Jiménez-Jorge and Amparo Larrauri designed the study. Silvia Jiménez-Jorge wrote the first draft of the manuscript and undertook the statistical analysis. Silvia Jiménez-Jorge, Salvador de Mateo and Amparo Larrauri participated in data analysis, writing and interpretation of the results. Francisco Pozo and Inmaculada Casas were responsible for the virus characterisation and contributed with the interpretation of the virological data. All authors participated in the interpretation of the data, contributed to the revision of the draft manuscript and approved the final version.

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# Interim estimates of 2013/14 influenza clinical severity and vaccine effectiveness in the prevention of laboratory-confirmed influenza-related hospitalisation, Canada, February 2014

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**During the 2013/14 influenza season in Canada, 631 of 654 hospitalisations for laboratory-confirmed influenza enrolled in sentinel hospitals were due to Influenza A. Of the 375 with known subtype, influenza A(H1N1) accounted for 357. Interim unmatched vaccine effectiveness adjusted for age and presence of one or more medical comorbidities was determined by test-negative case–control design to be 58.5% (90% confidence interval (CI): 43.9–69.3%) overall and 57.9% (90% CI: 37.7–71.5) for confirmed influenza A(H1N1).**

In the context of the first influenza season in Canada since the 2009 influenza pandemic to be marked by the predominant circulation of A(H1N1)pdm09 virus, we provide a critical interim assessment of overall and age-stratified 2013/14 influenza vaccine effectiveness against laboratory-confirmed influenza-associated hospitalisation. We describe the clinical and epidemiological characteristics of severe cases of influenza, defined as those requiring intensive care unit (ICU) admission, mechanical ventilation or resulting in death, who were hospitalised up to 8 February 2014 in the hospitals of the Public Health Agency of Canada/Canadian Institutes of Health Research (PCIRN) Serious Outcomes Surveillance (SOS) Network. The PCIRN SOS Network was established in 2009 to prospectively monitor annual seasonal influenza vaccine effectiveness in the prevention of laboratory-confirmed influenza-related hospitalisation in Canadian adults using a test-negative case–control design.

In Canada, annual influenza vaccine is recommended for all persons aged six months to 59 months or 65 years and older, and for persons of any age with medical comorbidities placing them at higher risk of severe influenza and its complications resulting in hospitalisation or death [1]. More than 98% of influenza vaccine

provided to adults is intramuscular split-virus trivalent inactivated influenza vaccine (TIV).

## Hospital-based surveillance

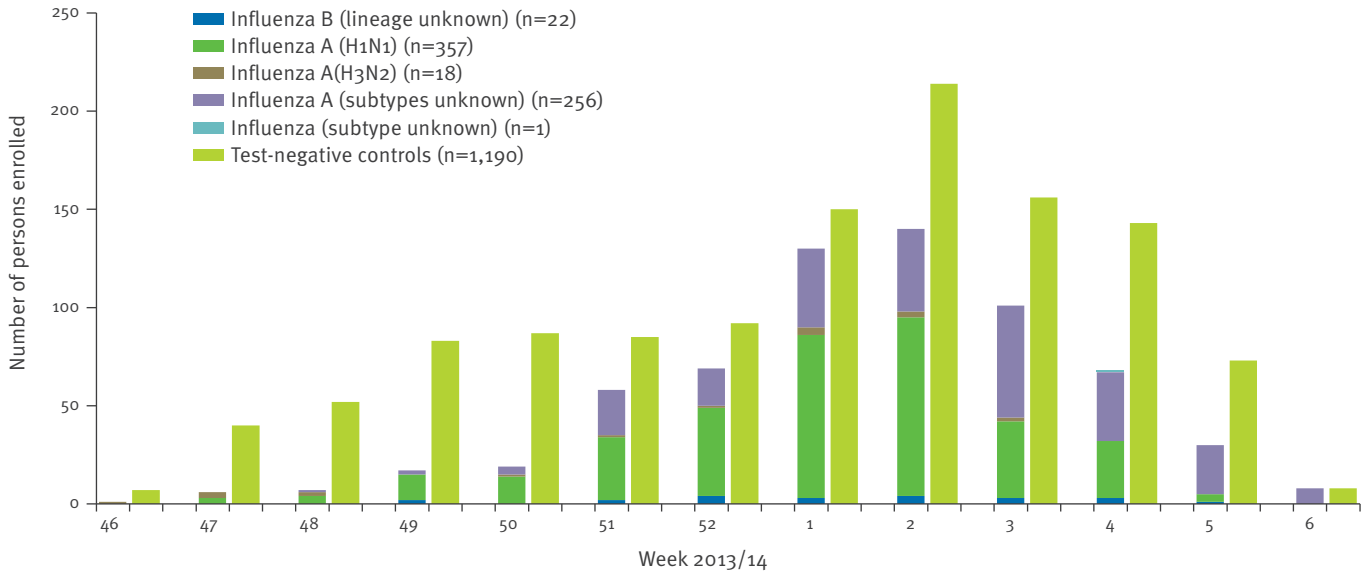
The PCIRN SOS Network comprises 40 adult academic and community hospitals in seven of the 10 Canadian provinces and three territories (New Brunswick, Nova Scotia, Quebec, Ontario, Manitoba, Alberta and British Columbia), accounting for ca 18,000 adult acute care hospital beds. For the 2013/14 season, beginning on 15 November 2013, trained SOS Network surveillance study staff (monitors) reviewed all daily admissions of people 16 years and older to medical and coronary ICU and medical wards (e.g. cardiology, respirology, family medicine, geriatric medicine, internal medicine) to identify eligible patients. Eligible patients were at least 16 years-old and admitted to participating hospitals with the following clinical presentations: pneumonia, acute exacerbation of chronic obstructive pulmonary disease or asthma, unexplained sepsis, any other respiratory infection or diagnosis, or any respiratory or influenza-like symptom (e.g. dypsnoea, cough, sore throat, myalgia, arthralgia, fever). One day per week, beginning when the local laboratory reported two or more positive influenza tests or when the local laboratory reported one or more positive influenza tests in two consecutive weeks, patients were screened who were admitted on that day with a triage temperature ≥37.5 °C associated with one of the following: acute coronary syndrome (e.g. myocardial infarction, unstable angina), any other cardiac diagnosis (e.g. atrial fibrillation, other arrhythmia, myocarditis), or stroke. In hospitals associated with the Toronto Invasive Bacterial Diseases Network (TIBDN), influenza testing was performed seven days per week as routine clinical practice. A temperature cut-off of ≥37.5 °C was used in this subgroup of patients in order to attempt to minimise false-negative influenza PCR results associated with lag between influenza infection and related cardiac and stroke hospitalisations.

Nasopharyngeal swabs were collected from all eligible patients as part of routine clinical care or by the SOS Network monitor. The specimens were tested for influenza by reverse-transcriptase PCR (RT-PCR) or viral culture in the local hospital or public health laboratory according to routine local testing procedures. SOS Network monitors collected detailed demographic information, medical and surgical history, details of presenting illness, hospitalisation details including management and healthcare utilisation, discharge and 30-day post-discharge outcomes. The 2013/14 influenza immunisation history was collected from the patient or their caregiver and, if possible, verified with their immunisation provider or an immunisation registry. Patients were considered immunised if they reported receipt of a current-season influenza vaccine more than two weeks before onset of their symptoms. Only the subset of severe, life-threatening influenza requiring ICU admission, mechanical ventilation or causing death is described here in detail.

The study was approved by the Research Ethics Boards of participating institutions and consent procedures

**Figure**

Laboratory-confirmed influenza cases and test-negative controls admitted to PCIRN SOS Network hospitals by week and virus subtype, 15 November 2013–8 February 2014 (n=1,844)




PCIRN SOS Network: Public Health Agency of Canada/Canadian Institutes of Health Research Serious Outcomes Surveillance Network.

**Table 1**

Clinical and demographic characteristics of laboratory-confirmed influenza cases and test-negative controls, Canada, 15 November 2013–8 February 2014 (n=1,844)

| Characteristics | Cases (N=654) n (%) | Controls (N=1,190) n (%) | Total (N=1,844) n (%) | p value[a] |
|---|---|---|---|---|
| Mean age (range) | 58.5 (16–98) | 67.9 (17–104) | 64.6 (16–104) | 0.00 |
| 16–49 years | 187 (28.6) | 162 (13.6) | 349 (18.9) | 0.00 |
| 50–64 years | 219 (33.5) | 282 (23.7) | 501 (27.2) | - |
| 65–75 years | 123 (18.8) | 287 (24.1) | 410 (22.2) | - |
| >75 years | 125 (19.1) | 459 (38.6) | 584 (31.7) | - |
| Female | 334 (51.1) | 608 (51.1) | 942 (51.1) | 1.00 |
| Inclusion criteria at enrollment | | | | |
| Pneumonia | 186 (28.4) | 524 (44.0) | 710 (38.5) | 0.00 |
| Acute exacerbation of COPD or asthma | 131 (20.0) | 283 (23.8) | 414 (22.5) | 0.07 |
| Unexplained sepsis | 16 (2.4) | 49 (4.1) | 65 (3.5) | 0.07 |
| Any other acute respiratory illness[b] | 414 (63.3) | 521 (43.8) | 935 (50.7) | 0.00 |
| Acute coronary syndrome[c,d] | 1 (0.2) | 4 (0.3) | 5 (0.3) | 0.66 |
| Any other cardiac diagnosis[c,d] | 4 (0.6) | 4 (0.3) | 8 (0.4) | 0.47 |
| Stroke[c,d] | 0 (0) | 1 (0.1) | 1 (0.1) | 1.00 |
| One or more comorbidities | 257/290 (88.6) | 351/370 (94.9) | 608/660 (92.1) | 0.004 |
| Received 2013/14 influenza vaccine | 227 (34.7) | 733 (61.6) | 960 (52.1) | 0.000 |

COPD: Chronic obstructive pulmonary disease.

[a] Cases versus controls.

[b] Includes those with any other respiratory infection or diagnosis or any respiratory or influenza-like symptom (e.g. dypsnoea, cough, sore throat, myalgia, arthralgia, fever).

[c] Includes only patients with a documented temperature of ≥37.5 °C at triage in the Emergency Department.

[d] Surveillance for acute coronary syndrome, other cardiac diagnoses and stoke was performed in SOS Network Sites outside of the Greater Toronto, Ontario sites only one day per week once influenza was known to be circulating locally.

followed local research ethics board requirements (clinical trial resgistration number: NCT01517191).

## Estimation of influenza vaccine effectiveness

All eligible patients hospitalised between 15 November 2013 and 8 February 2014 who underwent influenza testing and whose self-reported 2013/14 influenza immunisation status was available, were included in this interim analysis of vaccine effectiveness (VE). Hospitalised patients with a positive laboratory-test for influenza were defined as cases and those testing negative for influenza within seven days of onset of illness were defined as controls. Odds ratios (OR) for influenza vaccination among cases and controls were calculated and VE was estimated as (1–OR) x 100% by logistic regression adjusting for age and presence of one or more comorbidities. Overall adjusted VE and VE stratified by age (patients 65 years or older vs patients younger than 65 years) are presented.

## Interim estimates of influenza vaccine effectiveness

A total of 654 hospitalised influenza cases and 1,190 hospitalised test-negative controls were enrolled between 15 November 2013 and 8 February 2014 and included in the interim analysis. Weekly incidence of laboratory-confirmed influenza among adults hospitalised in SOS Network sites by subtype is shown in the Figure. Overall, 631 of 654 (96.5%) of admissions were due to influenza A; of those with a known subtype, influenza A(H1N1) accounted for 357 of 375 (95.2%).

The mean age of patients admitted with laboratory-confirmed influenza and of test-negative controls was 58.5 years (range: 16–98 years) and 67.9 years (17–104 years), respectively; 406 of 654 cases (62.1%) and 444 of 1,190 test-negative controls (37.3%) were under 65 years of age, and 51.1% in both groups were female (Table 1). Among those for whom a medical history was available, 88.6% of cases and 94.9% of test-negative controls had one or more medical comorbidities predisposing to complications of influenza. Some 34.7% of cases and 61.6% of test-negative controls reported receipt of the 2013/14 influenza vaccine.

The overall and age-stratified VE for the prevention of laboratory-confirmed influenza-related hospitalisation in Canadian adults are shown in Table 2. Overall interim VE of 2013/14 influenza vaccines in persons 16 years and older, adjusted for age and the presence of one or more medical comorbidities, was 58.5% (90% CI: 43.9–69.3). Among adults 65 years and older, the interim adjusted VE was 58.1% (90% CI: 35.4–72.8) and among adults under 65 years of age, the interim adjusted VE was 60.3% (90% CI: 39.4–74.0). Overall adjusted VE against confirmed influenza A(H1N1) was 57.9% (90% CI: 37.7–71.5).

## Clinical and epidemiological characteristics of patients with severe laboratory-confirmed influenza

Overall, 20.6% of the 654 hospitalised influenza cases admitted to SOS Network hospitals were severe, defined as requiring ICU admission, mechanical ventilation, or resulting in death. The mean age of severe cases was 58.6 years (22–98 years); 68.1% of severe cases were younger than 65 years (Table 3). Of the severe cases with available medical records, 84.7% had one or more comorbidities associated with increased risk of influenza complications. Of the severe cases, 33.9% reported receipt of the 2013/14 influenza vaccine (39.0% of cases with underlying comorbidity vs 5.3% of cases with no comorbidity; p=0.003). Until 8 February 2014, the overall mortality among hospitalised cases has been 4.9%, and of 32 deaths, 18 occurred in patients under the age of 65 years.

## Discussion

The 2013/14 influenza season in Canada has been dominated by influenza A(H1N1)pdm09 virus. Current data suggest that the virus circulating in Canada is well matched to the recommended vaccine strain; 84% of strains tested were A/California/07/2009-like influenza A(H1N1) [2]. Our interim VE estimates confirm moderate but clinically and statistically significant protection against serious influenza outcomes of clinical and public health importance. Our findings further suggest important potential changes in the epidemiology of severe, hospitalised influenza A(H1N1) compared with the 2009 pandemic, including an increase in the median age and the proportion of patients with comorbidity [3]. Furthermore, while overall mortality was 4.9%, similar to that observed during the 2009 influenza A(H1N1) pandemic [3], seasonal circulation of influenza A(H1N1) in 2013/14 was associated with need for admission to an ICU in 19% (90% CI:16.5–21.7%) of adults hospitalised in SOS Network hospitals compared with 29% during the pandemic, suggesting a shift in the epidemiology of influenza A(H1N1) to less severe disease more typical of seasonal influenza outbreaks. ICU admission was required in 12.7% (90% CI 10.5–15.1%) during the influenza B-dominated 2011/12 season and 14.9% (13.3–16.6%) during the influenza A(H3N2)-dominated 2012/13 season (PCIRN SOS Network, unpublished data).

Rates of ICU admission among patients admitted to hospital with laboratory-confirmed influenza during the pandemic are readily available from many countries and range from a low of 10% in the United Kingdom and the Netherlands to highs of 25% to 30% in the United States (US) [4-8]. Fewer studies report rates of ICU admission among patients admitted with laboratory-confirmed seasonal influenza, and rates vary widely by season and virus type/subtype [9-12]. Over three influenza seasons (2005–08) in the US, 14% of hospitalised influenza cases required ICU admission while in the 2010/11 season, ICU admission was required for 25.5% of influenza A(H1N1), 13.5% of A(H3N2) and 15.9% of influenza B cases in the US and 27% of influenza A and 15% of influenza B hospitalisations in Australia [9-11]. In Spain, 24.4% of hospitalised patients with influenza in 2010/11 required admission to ICU [12].

**Table 2**

Interim assessment of 2013/14 influenza vaccine effectiveness in the prevention of laboratory-confirmed influenza-related hospitalisation in adults, Canada, 15 November 2013–8 February 2014 (n=1,844)

| | Vaccine effectiveness estimate (%) | 90% confidence interval |
|---|---|---|
| **Unadjusted** | | |
| All influenza strains | | |
| Overall | 66.9 | 60.8–72.0 |
| Age ≥65 years | 59.4 | 47.9, –68.3 |
| Age <65 years | 57.3 | 45.2–66.6 |
| Confirmed influenza A(H1N1) | | |
| Overall | 66.8 | 59.2–73.0 |
| Age ≥65 years | 57.4 | 41.8–68.8 |
| Age <65 years | 59.7 | 45.2–70.4 |
| **Adjusted[a]** | | |
| All influenza strains | | |
| Overall | 58.5 | 43.9–69.3 |
| Age ≥65 years | 58.1 | 35.4–72.8 |
| Age <65 years | 60.3 | 39.4–74.0 |
| Confirmed influenza A(H1N1) | | |
| Overall | 57.9 | 37.7–71.5 |
| Age ≥65 years | 63.1 | 34.7–79.1 |
| Age <65 years | 54.2 | 21.6–73.2 |

[a] Adjusted for age and presence of one or more comorbidities.

The majority of patients requiring admission to an ICU, requiring mechanical ventilation or who died in SOS Network hospitals during the 2013/14 season had underlying medical comorbidities known to increase the risk of influenza complications and making them eligible for free influenza vaccine. Despite this, vaccine coverage in this high-risk group was only 39%; of those with severe disease, only 33% overall and 21.7% of those under 65 years of age had been vaccinated.

Our interim adjusted point estimate for VE against laboratory-confirmed influenza-related hospitalisation of 58.5% (90% CI: 43.9–69.3) is similar to that reported in the United States (61%; 95% CI: 52–68) [13] but lower than that reported by the outpatient sentinel surveillance network for prevention of medically attended laboratory-confirmed influenza (74%; 95% CI: 58–83) [14]. This is not surprising given that the population captured by the outpatient sentinel surveillance network is dominated by healthy working –age adults with comparatively few underlying medical comorbidities while the PCIRN SOS Network assesses VE in a cohort of hospitalised patients who were older (median age: 65 vs 37 years) and much more likely to have underlying medical comorbidities (92 vs 22%) [14,15]. Although lower than that observed for medically attended influenza in the community, effectiveness of the 2013/14

seasonal influenza vaccines in the prevention of serious, clinically important outcomes in adults of all ages was substantial, with reduction of influenza-associated hospitalisations of approximately 55–60%. As of 5 March 2014, the only other published study to report interim estimates of 2013/14 influenza VE against laboratory-confirmed hospitalisation is from Navarre, Spain, and reported lower overall and A(H1N1) specific VE [16]. However, potential differences in health systems, health seeking behaviour, number of cases and patterns of virus circulation (60% A(H3N2) and 40% A(H1N1) in the Navarre study) preclude a meaningful comparison with the present study.

Our findings are subject to at least two limitations. Firstly, as with other observational assessments of influenza vaccine effectiveness, the existence of bias and residual confounding cannot be excluded. We employed the test-negative case–control design, the currently preferred observational approach to assessing influenza vaccine effectiveness, to minimise misclassification and indication bias [17]. Secondly, while we are collecting data on numerous covariates in an attempt to adjust for potential confounders, these data were unavailable for the interim analysis. Consequently, the end-of-season, fully adjusted, VE estimates may be different. Although this has not been the experience of the Canadian outpatient sentinel surveillance network for the 2012/13 influenza season, the I-MOVE network in Europe reported important, but not statistically significant, differences between mid-season and end-of-season VE estimates [14,18].

Our findings highlight that important public health benefits of influenza vaccination are lost to poor immunisation coverage rates in some at-risk populations. Targeted public health messaging is important to encourage adults of all ages with medical comorbidity to seek annual influenza vaccination. The 2013/14 season has been unique in that it is the first predominant influenza A(H1N1) season since the 2009 pandemic, allowing us to characterise potential changes in the epidemiology and clinical severity of influenza A(H1N1) pdm09 as it becomes a seasonal virus. These data are important to guide public health risk communication and inform immunisation, prevention, and treatment recommendations for the 2014/15 season, which are currently being developed by National Immunization Technical Advisory Groups (NITAGS) in many countries around the world, including the Canadian National Advisory Committee on Immunization (NACI).

While the demonstrated effectiveness of 58% against serious disease due to influenza is modest, it arguably represents a significant clinical, public health and health service/cost benefit, given the burden of severe disease resulting in hospitalisation and its downstream complications including ICU admission, pneumonia, disability and death. While our data for the current vaccine suggests prevention of almost 60% of influenza hospitalisations with vaccination in a well matched influenza A(H1N1)-dominated season affecting predominantly younger adults with comorbidity, the unchanged vaccine recommended by the World Health Organization for the 2014/15 season may have very different effectiveness (better or worse) in the coming season depending on circulating strains and vaccine match. While an anticipated VE of 58% against hospitalisation is reasonable given the effectiveness observed in 2013/14, ongoing surveillance and mid-season estimates during the coming season will be critical to ensure that the vaccine is performing as anticipated and to provide early signal of possible drift, should the VE be lower than anticipated.

**Table 3**

Clinical and demographic characteristics of severe laboratory-confirmed influenza resulting in admission to an intensive care unit, mechanical ventilation or death, Canada, 15 November 2013–8 February 2014 (n=135)

| Characteristic | Death, ICU or mechanical ventilation (N=135) n (%) |
|---|---|
| Mean age (range) | 58.6 (22–98) |
| 16–49 years | 35 (25.9) |
| 50–64 years | 57 (42.2) |
| 65–75 years | 24 (17.8) |
| >75 years | 19 (14.1) |
| Female | 61 (45.2) |
| Received 2013/14 influenza vaccine | |
| Overall | 45 (33.3) |
| 16–49 years | 2 (5.7) |
| 50–64 years | 18 (31.6) |
| 65–75 years | 13 (54.2) |
| >75 years | 12 (63.2) |
| Influenza type | |
| Influenza A | 131 (97.0) |
| A(H1N1) | 84 (62.2) |
| A(H3N2) | 3 (2.2) |
| A (subtype unknown) | 44 (32.6) |
| Influenza B | 4 (3.0) |
| One or more comorbidity | |
| Yes[a] | 105/124 (84.7) |
| Diabetes (no end-organ complications) | 33/124 (26.6) |
| Diabetes with complications | 8/124 (6.5) |
| Cardiac disease | 39/118 (33.1) |
| Pulmonary disease | 50/124 (40.3) |
| Asthma | 13/124 (10.5) |
| COPD | 28/124 (22.6) |
| Renal disease | 14/121 (11.6) |
| Neuromuscular disease | 16/121 (13.2) |
| Cancer | 20/121 (16.5) |
| No | 19/124 (15.3) |
| Unknown | 11/135 (8.1) |
| Deaths | 32/654 (4.9) |
| Mean age (range) | 64.8 (28–98) |
| 16–49 years | 6 (18.8) |
| 50–64 years | 12 (37.5) |
| 65–75 years | 5 (15.6) |
| ≥75 years | 9 (28.1) |

COPD: Chronic obstructive pulmonary disease; ICU: intensive care unit.

[a] Comorbidities reported as rates among those with available data; denominator represents number of patients in whom this data point was available.

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## Conflict of interest

VS, FH and BI are employed by the GlaxoSmithKline Group of Companies. VS reports ownership of stock options and/or restricted shares in the GlaxoSmithKline Group of Companies; SAM research grants from GlaxoSmithKline, Pfizer, Sanofi Pasteur; JML research grants from GlaxoSmithKline and Sanofi Pasteur and other from AstraZeneca; JM personal fees from GlaxoSmithKline, Medimmune, Merck, Sanofi Pasteur; JP GlaxoSmithKline, Pfizer and personal fees from Merck and Pfizer; LV research grants from GlaxoSmithKline, Pfizer, Optimer, Cubist and Merck, and personal fees from Merck, Optimer and Cubist. This study is funded by the Public Health Agency of Canada, the Canadian Institutes of Health Research, and through a Collaborative Research Agreement with GlaxoSmithKline Biologicals SA.

## Authors' contributions

SAM, VS, MA, AA, TFH, FH, DMC, LY, AM were involved in the conception and design of the study; SAM, GB, WB, FDM, KG, SH, KK, JML, PLW, BL, ML, JM, AEM, AP, JP, DR, MS, SS, DS, GS, ST, LV, DW, and AM were responsible for acquisition of data; TFH, JL, ME conducted/supervised the PCIRN SOS Network central laboratory; SAM, VS, FH, DMC, AM, LY analysed and interpreted the data; SAM drafted the manuscript; all authors revised the manuscript critically for important intellectual content; all authors reviewed and approved the final draft of the manuscript.

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# Epidemiology of tuberculosis in big cities of the European Union and European Economic Area countries

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This cross-sectional survey aimed to examine the epidemiology of tuberculosis (TB) in European Union (EU) and European Economic Area (EEA) cities with populations greater than 500,000. National TB programme managers were asked to provide data on big city population size, total number of notified TB cases in big cities and national notification rate for 2009. A rate ratio was calculated using the big city TB notification rate as a numerator and country TB notification rate, excluding big city TB cases and population, as a denominator. Twenty of the 30 EU/EEA countries had at least one big city. Pooled rate ratios were 2.5, 1.0, and 0.7 in low-, intermediate- and high-incidence countries respectively. In 15 big cities, all in low-incidence countries, rate ratios were twice the national notification rate. These data illustrate the TB epidemiology transition, a situation whereby TB disease concentrates in big cities as national incidence falls, most likely as a result of the higher concentration of risk groups found there. This situation requires targeted interventions and we recommend that big city TB data, including information about patients' risk factors, are collected and analysed systematically, and that successful interventions are shared.

## Introduction

Tuberculosis (TB) notification rates in the European Union (EU) have been declining at a mean annual rate of 4.4% since 2006, and in 2010 there were 73,996 TB cases reported by the 27 EU Member States and the three European Economic Area (EEA) countries (Iceland, Liechtenstein and Norway) [1]. This resulted in notification rates below 100 per 100,000 population in all EU Member States for the first time in 2010. These national and EU-wide figures demonstrate the progress made towards the target of elimination, defined as less than one infectious (sputum smear-positive) case per 1,000,000 population [2]. However, they hide some of the wide variations that exist between and within countries.

Several publications have highlighted the higher notification and incidence rates in EU/EEA big cities or metropolitan areas, compared to non-urban areas, which is particularly evident among certain high-risk groups for TB overrepresented in big cities, including migrants from high-incidence countries, homeless people and drug and alcohol users [3–14]. The nomenclature used to describe major urban conurbations is variable within the literature, and includes big or large city, metropole or metropolitan area, urban area. The definition is often based on population size or density criteria. Cities are administrative areas (municipalities), while metropolitan areas usually combine urban agglomeration with peripheral zones that are not necessarily urban in character, but are closely bound to the centre by employment or commerce [15]. Urban and suburban areas can also share the general big city social structures underpinning the congregation of urban high-risk groups.

TB surveillance in Europe does not provide specific information on the epidemiology of TB in big cities, and data are only available routinely within countries and not readily accessible for international comparison. To inform the preparation of the consensus statement, which examined the structural determinants of TB in EU/EEA big cities, as well as provided

recommendations for big city TB control [16], a survey of national TB programme managers was conducted. This cross-sectional survey aimed to provide detailed information of the epidemiology of TB in EU/EEA big cities, allowing an analysis of the case distribution and infection rates within low-, intermediate- and high-incidence EU/EEA countries and their big cities.

## Methods

### Cross-sectional survey among national tuberculosis programme managers

For the purpose of this work we defined a big city as any municipality in the EU/EEA which had more than 500,000 inhabitants in 2009.

World Health Organization (WHO) national TB programme managers in EU/EEA countries were emailed by one of the authors (GdV) during the period from April 2011 to October 2012 using a list provided by the WHO Regional Office for Europe. TB programme managers received a form containing big city population size data, the total number of national notified TB cases, and national notification rate for their country in 2009. These pre-populated data were taken from various sources. City population estimates were taken from the Eurostat Population and living conditions in Urban Audit cities (core city) [17] or where not available other Internet sources such as Wikipedia were used. Country population sizes were taken from the *Tuberculosis Surveillance in Europe 2009* report [18]. The total number of national notified TB cases in 2009 and the national notification rate were taken from the *Tuberculosis Surveillance and monitoring in Europe 2012* report [1]. National TB programme managers were asked to verify (or change as necessary) this pre-populated data, or to send this information on to appropriate public health officials responsible for TB control in the big city under consideration. They were also asked to provide the number of TB cases for each big city identified within their country in 2009. Data received back from the national TB programme managers, or public health authorities responsible for TB control in these big cities, were collated in an Excel spreadsheet.

To examine the effect of big cities on TB incidence, we calculated rate ratios using the big city TB notification rate as a numerator and the country TB notification rate, excluding big city TB cases and population, as a denominator. National and big city TB notification rates and rate ratios were calculated in Stata (StataCorp LP, College Station, TX, USA) version 12.

Data were presented separately for low-, intermediate- and high-incidence EU/EEA countries and their big cities. Various definitions for low-incidence and high-incidence countries exist. The European Centre for Disease Prevention and Control (ECDC) defines countries with a TB incidence rate of ‹20 TB cases per 100,000 population as low-incidence countries entering the phase of elimination [1]. For this study we classified countries into low-incidence countries (‹20 notifications per 100,000 population), mainly in western EU/EEA, and intermediate (20-50 notifications per 100,000) and high-incidence countries (›50 notifications per 100,000), mainly in the central and eastern EU.

### Data from the tuberculosis control in European Union big cities working group

Annual notification rates for six selected big cities, available for the last 20 years, were collected in order to examine and exemplify time trends within these cities. Selection was based on participation in the working group, availability of data and its illustrative power to show a stable, declining or increasing trend. Two of these big cities with five-year inner city data available were selected to demonstrate the variation of TB notification rates within their big cities.

## Results

### Current epidemiology of tuberculosis in big cities – cross-sectional survey results

From the 30 EU/EEA countries, 20 had at least one big city (15/23 low-incidence, 3/5 intermediate and 2/2 high-incidence countries), with 54 big cities in total, 45 in low-incidence, seven in intermediate and two in high-incidence countries. All national TB programme managers or public health authorities from these big cities responded.

The population in big cities represented 12.4% of the total EU/EEA population. The highest notification rates in big cities in low-incidence countries were observed in Birmingham and London, United Kingdom (58.0, 44.4 respectively), followed by Brussels, Belgium (29.9), and Barcelona, Spain (27.0), all higher or considerably higher compared to their national TB notification rates (Table 1). The highest notification rates in big cities in intermediate and high-incidence countries were observed in Bucharest, Romania (87.1) and Riga, Latvia (43.0), followed by Sofia, Bulgaria (36.6) and Vilnius, Lithuania (31.9), all lower than their national TB notification rates.

The highest rate ratios (big city notification rate more than twice the national notification rate) were found in 15 big cities, all in low-incidence countries. Birmingham had the highest rate ratio followed by Brussels; London; and Rotterdam, the Netherlands (4.0, 3.2, 3.0 and 3.0 respectively); Copenhagen, Denmark; Milan, Italy; Oslo, Norway; Paris, France; and Turin, Italy (all 2.8); Amsterdam, the Netherlands (2.7); Rome, Italy (2.5),; Frankfurt, Germany (2.4); Cologne, Germany (2.3); Athens, Greece (2.2); and Genoa, Italy (2.0).

Table 2 shows the aggregated population size, TB caseload and notification rates in EU/EEA countries and big cities according to notification rate at country level. In 2009, the TB notification rate across the EU/EEA was 15.8 per 100,000 inhabitants and 22.3 in big

## Table 1

Population size, tuberculosis cases and notification rates in low-, intermediate- and high-incidence European Union/European Economic Area countries and their big cities (>500,000 population), and rate ratio for big cities, 2009 (20 countries, 54 cities)

| Country | Population | TB cases | Notification rate | Big city | Population | TB cases | Notification rate | Rate ratio[a] |
|---|---|---|---|---|---|---|---|---|
| Low-incidence countries (TB incidence <20 per 100,000 population) | | | | | | | | |
| Austria | 8,355,260 | 698 | 8.4 | Vienna | 1,698,957 | 256 | 15.1 | 1.8 |
| Belgium | 10,666,866 | 994 | 9.3 | **Brussels** | **1,068,532** | **320** | **29.9** | **3.2** |
| Czech Republic | 10,467,542 | 695 | 6.6 | Prague | 1,233,211 | 128 | 10.4 | 1.6 |
| Denmark | 5,511,451 | 337 | 6.1 | **Copenhagen** | **667,228** | **113** | **16.9** | **2.8** |
| Finland | 5,326,314 | 417 | 7.8 | Helsinki | 583,350 | 58 | 9.9 | 1.3 |
| France | 62,131,000[b] | 5,114[b] | 8.2 | **Paris** | **2,199,500** | **515** | **23.4** | **2.8** |
| | | | | Marseille | 852,396 | 103 | 12.1 | 1.5 |
| Germany | 82,002,356 | 4,419 | 5.4 | Berlin | 3,442,675 | 269 | 7.8 | 1.4 |
| | | | | Hamburg | 1,774,224 | 178 | 10.0 | 1.9 |
| | | | | Munich | 1,330,440 | 103 | 7.7 | 1.4 |
| | | | | Hannover | 1,130,262[c] | 70 | 6.2 | 1.1 |
| | | | | **Cologne** | **998,105** | **126** | **12.6** | **2.3** |
| | | | | **Frankfurt** | **671,927** | **87** | **12.9** | **2.4** |
| | | | | Bremen | 661,716 | 57 | 8.6 | 1.6 |
| | | | | Stuttgart | 601,646 | 49 | 8.1 | 1.5 |
| | | | | Dusseldorf | 586,217 | 57 | 9.7 | 1.8 |
| | | | | Dortmund | 581,308 | 47 | 8.1 | 1.5 |
| | | | | Essen | 572,569 | 21 | 3.7 | 0.7 |
| | | | | Dresden | 518,862 | 30 | 5.8 | 1.1 |
| | | | | Leipzig | 517,052 | 44 | 8.5 | 1.6 |
| | | | | Nuremberg | 503,673 | 44 | 8.7 | 1.6 |
| Greece | 11,260,402 | 594 | 5.3 | **Athens** | **745,514** | **91** | **11.5** | **2.2** |
| Hungary | 10,030,975 | 1,407 | 14.0 | Budapest | 1,695,000 | 321 | 18.9 | 1.4 |
| Italy | 60,045,068 | 4,244 | 7.1 | **Rome** | **2,724,347** | **487** | **17.9** | **2.5** |
| | | | | **Milan** | **1,650,000[c]** | **327** | **19.8** | **2.8** |
| | | | | Naples | 963,661 | 68 | 7.1 | 1.0 |
| | | | | **Turin** | **909,538** | **183** | **20.1** | **2.8** |
| | | | | Palermo | 659,433 | 51 | 7.7 | 1.1 |
| | | | | **Genoa** | **611,171** | **87** | **14.2** | **2.0** |
| Netherlands | 16,485,787 | 1,157 | 7.0 | **Amsterdam** | **755,605** | **143** | **18.9** | **2.7** |
| | | | | **Rotterdam** | **699,609** | **128** | **21.3** | **3.0** |
| Norway | 4,799,252 | 358 | 7.5 | **Oslo** | **575,475** | **121** | **21,0** | **2.8** |
| Spain | 45,828,172 | 7,592 | 16.6 | Madrid | 3,255,944 | 580 | 17.8 | 1.1 |
| | | | | Barcelona | 1,455,000 | 393 | 27.0 | 1.6 |
| | | | | Valencia | 814,208 | 177 | 21.7 | 1.3 |
| | | | | Seville | 703,206 | 107 | 15.2 | 0.9 |
| | | | | Zaragoza | 674,317 | 117 | 17.4 | 1.0 |
| | | | | Malaga | 568,305 | 93 | 16.4 | 1.0 |
| Sweden | 9,256,347 | 617 | 6.7 | Stockholm | 810,120 | 39 | 4.8 | 0.7 |
| | | | | Gothenburg | 500,197 | 49 | 9.8 | 1.5 |
| United Kingdom | 61,179,256 | 8,917 | 14.6 | **London** | **7,753,555** | **3,440** | **44.4** | **3.0** |
| | | | | Glasgow | 878,135 | 213 | 24.3 | 1.7 |
| | | | | **Birmingham** | **687,700** | **399** | **58.0** | **4.0** |
| | | | | Leeds | 787,700 | 124 | 15.7 | 1.1 |
| | | | | Sheffield | 547,000 | 80 | 14.6 | 1.0 |
| Intermediate-incidence countries (TB incidence 20–50 per 100,000 population) | | | | | | | | |
| Bulgaria | 7,606,551 | 2,910 | 38.3 | Sofia | 1,249,798 | 457 | 36.6 | 1.0 |
| Latvia | 2,261,294 | 978 | 43.2 | Riga | 709,145 | 305 | 43.0 | 1.0 |
| Poland | 38,135,876 | 8,236 | 21.6 | Warsaw | 1,711,466 | 304 | 17.8 | 0.8 |
| | | | | Krakow | 754,853 | 73 | 9.7 | 0.4 |
| | | | | Lodz | 744,541 | 187 | 25.1 | 1.2 |
| | | | | Wroclaw | 632,240 | 175 | 27.7 | 1.3 |
| | | | | Poznan | 556,022 | 70 | 12.6 | 0.6 |
| High-incidence countries (TB incidence >50 per 100,000 population) | | | | | | | | |
| Lithuania | 3,349,872 | 2,081 | 62.1 | Vilnius | 558,165 | 178 | 31.9 | 0.5 |
| Romania | 21,498,616 | 23,164 | 107.7 | Bucharest | 1,944,226 | 1,694 | 87.1 | 0.8 |

TB: :tuberculosis.

[a] Rate ratio calculated using the big city TB notification rate as a numerator and country TB notification rate, excluding big city TB cases and population, as a denominator.

[b] Excluding overseas districts of France.

[c] Populations of Hannover and Milan are for the greater municipal area/conglomerate.

Cities shown in blue are those with a rate ratio greater than or equal to 2.0.

**Table 2**

Aggregated population size, number of notified tuberculosis cases and notification rates stratified by tuberculosis notification rate and rate ratios of big city and country incidences, European Union/European Economic Area countries and their big cities, 2009 (30 countries, 45 cities)

| Notification (incidence rate)[a] | EU/EEA countries | | | | EU/EEA big cities | | | | Rate ratio[b] (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | Number of countries | Population | TB cases | Notification rate[a] [range] | Number of big cities | Population | TB cases | Notification rate [range] | |
| Low[c] (0–20 cases) | 23 | 417,299,635 | 38,868 | 9.3 [5.3–16.6] | 45 | 53,562,242 | 10,493 | 19.6 [3.7–58.0] | 2.5 [2.5–2.6] |
| Intermediate (20–50 cases) | 5 | 59,971,386 | 15,406 | 25.7 [21.6–43.2] | 7 | 6,358,065 | 1,571 | 24.7 [9.7–43.0] | 1.0 [0.9–1.0] |
| High (>50 cases) | 2 | 24,848,488 | 25,245 | 101.6 [62.1–108.2] | 2 | 2,502,391 | 1,872 | 74.8 [31.9–87.1] | 0.7 [0.7–0.8] |
| Total | 30 | 502,119,509 | 79,519 | 15.8 [5.3–108.2] | 54 | 62,422,698 | 13,936 | 22.3 [3.6–87.1] | 1.5 [1.5–1.5] |

CI: confidence interval; EU: European Union; EEA: European Economic Area; TB: tuberculosis

Low-incidence countries are defined as having <20 notifications per 100,000 population; intermediate-incidence countries as having 20–50 notifications per 100,000 population; and and high-incidence countries countries as having >50 notifications per 100,000 population.

[a] Cases per 100,000 population per year.

[b] A rate ratio was calculated using the big city TB notification rate as a numerator and country TB notification rate as a denominator, after the exclusion of big cities population and TB cases from this national figure.

[c] Excluding overseas districts of France.

cities, resulting in a rate ratio of 1.5. Pooled rate ratios were 2.5, 1.0, and 0.7 in low-, intermediate- and high-incidence countries respectively. Big cities of EU/EEA low-incidence countries accounted for 27.0% (10,493 of 38,868) of the notified TB cases while only 12.8% of the general population lived in these cities.

### Tuberculosis control in big cities case studies

Figure 1 presents examples of trends in TB notification rates over the past two decades in selected EU big cities. In the past two decades Barcelona and Paris notification rate has reduced from almost 70 per 100,000 population to around 25 while London has experienced almost a doubling of notification rates since 1990 from around 24 per 100,000 population to 45. Brussels continues to have high notification rates between 30 and 40 per 100,000 population, while Berlin, Germany, maintains a low notification rate of around 10, although an increase was observed in the past two years. In Rotterdam, the TB notification rate initially almost doubled from 1990 and reached 29 per 100,000 in 2003 but then the increasing trend reversed to a rate of 15 per 100,000 in 2011.

Notification rates also vary within different districts of a city. In London and in Rotterdam, levels were highest in the inner city districts (Figure 2). However, this is not consistent across all EU big cities; for example in Stockholm, Sweden, socially disadvantaged groups tend to live outside the city, in suburbs with higher notification rates than for the city itself (personal communication, J Jonsson, December 2011).

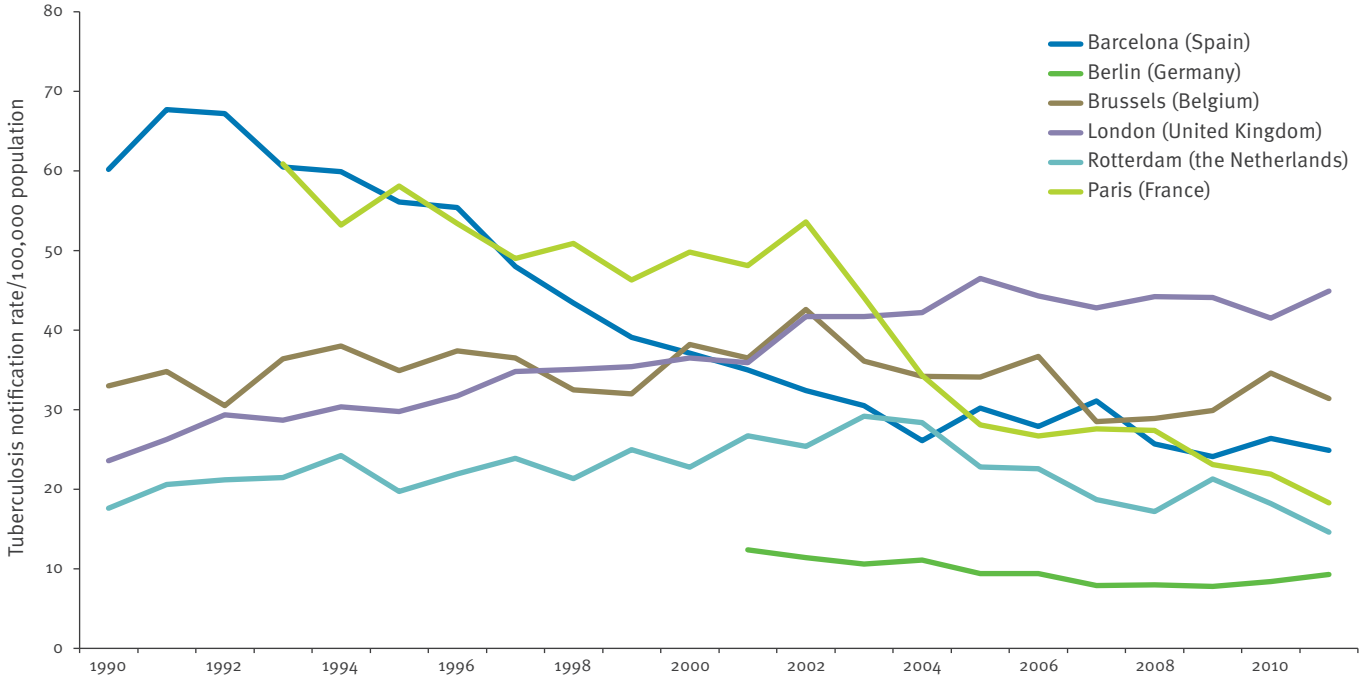
## Discussion

This study presents the results of a cross-sectional survey of national and big city TB programme managers, examining the distribution of TB cases and rates within EU/EEA countries and big cities. In 2009, 15 out of 54 EU/EEA big cities had a notification rate two times greater than the national notification rate and all were in low-incidence countries. The TB notification rate across the EU/EEA was 15.8 per 100,000 population (excluding overseas districts of France) compared to 22.3 in the big cities. In low-incidence EU/EEA countries, 27.0% of TB cases lived in big cities, compared to only 12.8% of the general population residing there. These data illustrate the high levels of TB found in EU/EEA big cities that are not obvious when examining national data alone. Analysis of available long-term data for EU/EEA big cities show that while there is a general downward trend, some big cities such as London have seen an increase in notifications over recent years.

In the United States (US) a study examined all incident cases of TB reported to the Centers for Disease Control and Prevention's National Tuberculosis Surveillance System (NTSS) from 2000 to 2007 [19]. This study found that a significant TB burden occurs in large US cities with 36% of all US TB patients living in 48 cities compared with only 15% of the general US population. TB incidence rates in these cities (12.1/100,000) were four times higher than that in the US when excluding the cities (3.8/100,000).

**Figure 1**

Trends of tuberculosis notification rates in selected big cities in low-incidence European Union/European Economic Area countries, 1990–2011




Selection was based on participation in the European Union big cities working group, availability of data and its illustrative power to show a stable, declining or increasing trend. Paris data available from 1993, Berlin data available from 2001.

A European study conducted in 1999–2000 contacted national TB coordinators in western European countries (or their public health counterparts in the appropriate cities) and asked them to provide TB epidemiological data [5]. Notification rates in cities were found to range from less than 10 per 100,000 population to 70. Notification rates were more than double the overall rate for the country in eight of the cities (Brussels; Copenhagen; Paris; Thessaloniki, Greece; Milan; Amsterdam; The Hague, the Netherlands; and London). These findings were consistent with those of our study which also found Brussels, Copenhagen, Paris, Milan, Amsterdam, and London to have a rate ratio of greater than two (Thessaloniki and The Hague did not meet our criteria for big city). In addition to the disparities that exist between levels within countries and their big cities, there is also variation within big cities themselves within different districts of a city.

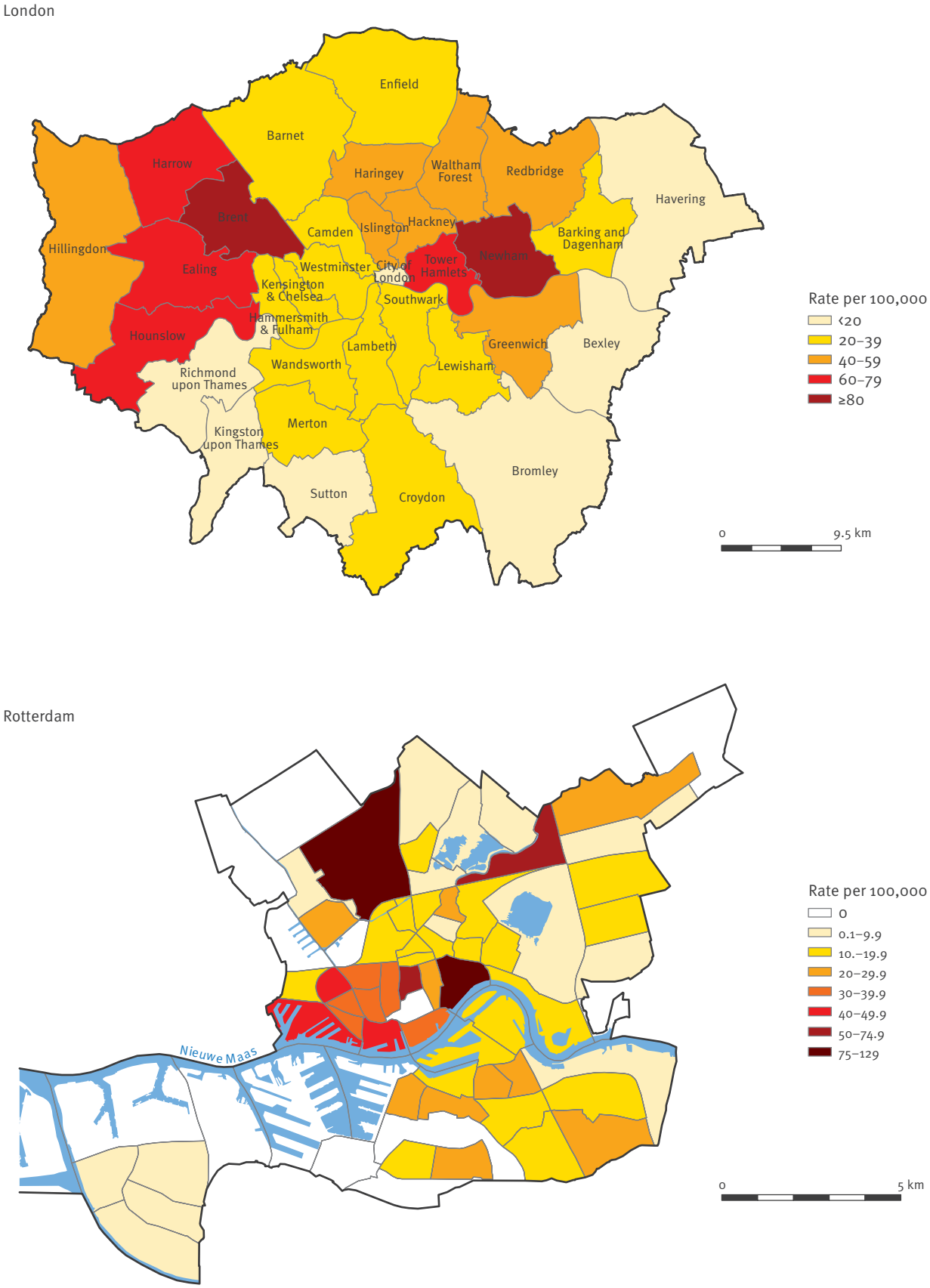
Our study used a narrow definition of TB in big cities to refer to cases residing within the administrative boundaries of a municipality, although for two big cities (Hannover, Germany; and Milan) information was not available. TB case ascertainment is a dynamic process both in EU/EEA countries and in their big cities, so the actual number of cases and notification rate may change over time. Since we collected the data on TB in big cities at approximately the same time as EU/EEA countries uploaded the revised 2009 data to ECDC, presented in the 2012 report [1], we optimised comparison of data. Our study did not collect data on risk factors of urban and national TB cases, which may further explain the urban-rural difference found in this study. We also did not gather information on TB control strategies and resources, which may differ in urban and rural areas, and effect case detection and notification levels.

Factors contributing to the high notification rates in western EU/EEA big cities are likely to be related to the relatively high proportion of immigrants from high-incidence countries, outbreaks among homeless people, drug users and alcoholics, and on-going transmission to other urban populations [5,10,19,20]. Factors such as the high population density in big cities, the high prevalence of congregate settings, population pockets in big cities with lower socio-economic status [21], and at times inadequate public health responses [22–24], are also likely to contribute to higher TB notification rates in big cities.

Our study shows that with TB notification rates declining to less than 20 per 100,000 population, in most EU/EEA countries, TB rates in big cities remain higher than the national notification rate. Our data also illustrate the TB epidemiology transition: a situation whereby TB

**Figure 2**

Average tuberculosis notification rates per 100,000 population and by borough or postal code area in London and Rotterdam, 2007-2011



disease concentrates in big cities as national incidence falls, most likely as a result of the risk groups found there. We expect that countries going down from high and intermediate incidence to low-incidence are likely to experience the same phenomenon and should consider this changing epidemiological situation in their TB control programmes in a timely manner. To tackle this problem we recommend that big city TB data, including risk profiles of patients, are collected and analysed systematically and that interventions to control TB successfully in big cities are shared. The accompanying consensus statement on TB goes some way to ensuring consistency in approaches that are required [16].

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## Authors' contributions

GdV wrote the first draft of the manuscript. All authors contributed to the editing of the paper and have seen and agreed the final version.

## Conflict of interest

None declared.

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# Successful control of a hospital-wide outbreak of OXA-48 producing Enterobacteriaceae in the Netherlands, 2009 to 2011

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On 31 May 2011, after notification of *Klebsiella pneumoniae* (KP)$_{OXA-48;CTX-M-15}$ in two patients, nosocomial transmission was suspected in a Dutch hospital. Hospital-wide infection control measures and an outbreak investigation were initiated. A total of 72,147 patients were categorised into groups based on risk of OXA-48 colonisation or infection, and 7,527 were screened for Enterobacteriaceae$_{OXA-48}$ by polymerase chain reaction (PCR). Stored KP isolates (n=408) were retrospectively tested for OXA-48 and CTX-M-1 group extended-spectrum beta-lactamases (ESBL). 285 KP isolates from retrospective and prospective patient screening were genotyped by amplified fragment length polymorphism (AFLP). 41 isolates harbouring different Enterobacteriaceae species were analysed by plasmid multilocus sequence typing (pMLST). No nosocomial transmission of Enterobacteriaceae$_{OXA-48}$ was detected after 18 July 2011. Enterobacteriaceae$_{OXA-48}$ were found in 118 patients (KP (n=99), *Escherichia coli* (n=56), ≥1 Enterobacteriaceae$_{OXA-48}$ species (n=52)), of whom 21 had clinical infections. 39/41 (95%) of OXA-48 containing plasmids were identical in pMLST. Minimum inhibitory concentrations (MICs) of KP$_{OXA-48}$ and *E. coli*$_{OXA-48}$ for imipenem and meropenem ranged from ≤1 to ≥16 mg/L, and 153/157 (97%) had MIC >0.25 mg/L for ertapenem. AFLP identified a cluster of 203 genetically linked isolates (62 KP$_{OXA-48;CTX-M15}$; 107 KP$_{CTX-M-15}$; 34 KP$_{OXA-48}$). The 'oldest' KP$_{CTX-M-15}$ and KP$_{OXA-48}$ clonal types originated from February 2009 and September 2010, respectively. The last presumed outbreak-related KP$_{OXA-48}$ was detected in April 2012. Uncontrolled transmission of KP$_{CTX-M-15}$ evolved into a nosocomial outbreak of KP$_{OXA-48;CTX-M15}$ with large phenotypical heterogeneity. Although the outbreak was successfully controlled, the contribution of individual containment measures and of the hospital relocating into a new building just before outbreak notification was impossible to quantify.

## Introduction

The number of infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBL), such as for example those with CTX-M-1 group ESBL and/or carbapenemases is rapidly increasing worldwide [1-3]. Carbapenem resistance in Enterobacteriaceae is mainly caused by production of one of three groups of carbapenemases: Ambler class A (*Klebsiella pneumoniae* carbapenemase (KPC)), B (metallo-beta-lactamases, e.g. Verona integron-encoded metallo-beta-lactamase (VIM), New Delhi metallo-beta-lactamase (NDM)), and D (oxacillinases, e.g. OXA-48), usually in combination with ESBL-production.

OXA-48 oxacillinase was identified for the first time in a *K. pneumoniae* isolate from Istanbul, Turkey in 2001 [4], and patients infected or carrying such bacteria have been reported from Asia [5], north Africa [6-8], South Africa [9], Europe [10-12] and north America [13]. OXA-48 has also been described in *Escherichia coli*, *Enterobacter cloacae*, and *Citrobacter freundii* and hospital outbreaks have been reported across Europe and the northern part of Africa [6,7,10-12,14,15]. Hospital outbreaks in western-European countries, such as France and Spain have been linked to transfer of patients from hospitals in endemic countries, such as Turkey and Morocco [8,12,16,17].

In 2008 sporadic events of *K. pneumoniae* with ESBL phenotypes occurred in a Dutch hospital (hospital A). Subsequently, in February 2009 two clonal type *K. pneumoniae*$_{CTX-M-15}$ isolates were identified and the occurrence of this clonal type gradually increased since, despite implementation of several control measures to interrupt transmission.

In May 2011, *K. pneumoniae*$_{OXA-48;CTX-M-15}$ was notified in two patients after discharge from hospital A. As

*K. pneumoniae*$_{OXA-48}$ were only detected only sporadically in Dutch hospitals, the coincidence of this finding was considered highly suggestive for nosocomial transmission. This initiated a retrospective and prospective investigation to determine the potential spread and the number of patients colonised and/or infected with Enterobacteriaceae harbouring OXA-48. There was, in parallel, implementation of a hospital-wide outbreak containment strategy. Moreover microbiological studies were undertaken to determine associations between *K. pneumoniae*$_{OXA-48}$ and previously identified *K. pneumoniae*$_{CTX-M-15}$ isolates. Here, we describe the sequence of events, effects of intervention and results from microbiological investigation of the, to our knowledge, largest nosocomial outbreak of *K. pneumoniae*-$_{OXA-48}$ in Europe so far.

## Methods

### Setting

Hospital A is a secondary care hospital. Until 16 May 2011 care was provided at two locations. Acute care was given in location 1, with 340 beds and a 12-bed intensive care unit (ICU), and non-acute care was concentrated in location 2 with 242 beds and a seven-bed ICU. On 16 May 2011, the entire hospital was moved to a new building physically separated from the two past locations. Coincidentally to the move, the total number of beds provided by the hospital changed, whereby the new building comprises 602 beds and 16 ICU beds.

Following the notification of two patients on 31 May 2011, with *K. pneumoniae*$_{OXA-48;CTX-M_{15}}$ growing from clinical cultures, after hospitalisation in hospital A, an outbreak investigation was initiated on 1 June 2011.

### Infection control measures

As soon as the outbreak investigation started, the hospital received immediate assistance in outbreak control from four members of the National Institute of Health and the Environment and from three experts of the department of Medical Microbiology of the University Medical Center (UMC) Utrecht from 30 June 2011 onwards. The Dutch guideline for highly resistant microorganisms (HRMO) was implemented throughout the hospital starting from 30 June [18]. This included patient screening for Enterobacteriaceae$_{OXA-48}$ and pre-emptively isolating patients from defined risk categories (see below) upon admission. Patients with HRMO were also isolated.

Cohorting of dedicated nursing staff was not applied. However, communication between the departments of medical microbiology and infection prevention and other healthcare personnel was intensified. Adherence to basic infection control measures was pursued through regular instruction meetings at hospital wards, but was not quantified. During the initial phases of outbreak control, between 7 and 27 June 2011, all ICU staff members (80 nurses and 16 physicians) were screened using both throat and rectal swabs, and none were found positive for OXA-48. In addition, 26 environmental samples were obtained in ICU in July 2011 (including air filters and objects in rooms of OXA-48 carriers). As these environmental samples tested negative for OXA-48, cleaning procedures, which after 1 June had remained as prior to the outbreak, were not subsequently changed and elimination of colonisation in patients was not attempted. There was no intervention on antibiotic stewardship, and patients with infections were treated according to standard antimicrobial treatment policy. Healthcare personnel and environmental screening was not repeated.

### Categorisation of patients

Based on the emergence of *K. pneumoniae* with ESBL phenotype in hospital A since early 2009, start and end of the outbreak period were – arbitrarily – defined as 1 July 2009 and 18 July 2011, respectively (see results).

Patients with a clinical culture (taken because of a clinical suspicion of infection by treating physician) or screening culture (taken with the purpose of detecting OXA-48 carriage, without a clinical suspicion of infection) taken after 1 January 2009, containing PCR-confirmed OXA-48 positive Enterobacteriaceae, excluding *Shewanella spp.*, were considered OXA-48 carriers. The status of OXA-48 carrier was maintained unless six consecutive screening cultures from the patient performed every two months were negative (i.e. 1 year negative).

Other patients were classified in three groups based on risk of OXA-48 colonisation or infection (Table 1).

- High-risk patients comprised (i) patients who had shared a hospital room with an OXA-48 carrier during the outbreak period or had been admitted to a room from which an OXA-48 carrier had been discharged within the previous two hours and (ii) all patients identified since 1 July 2009 with Enterobacteriaceae having minimum inhibitory concentrations (MICs) for imipenem ≥2mg/L or meropenem ≥0.5 mg/L, as detected by the Vitek 2 system (bioMérieux, Marcy l'Etoile, France). If the later patients had been hospitalised, individuals who had shared a room with such patients or had been in the same room within two hours after discharge and/or transfer to another room of such patients were also considered as belonging to the high risk group.
- Medium-risk patients comprised patients who had been admitted to hospital A during the outbreak period, but did not meet high-risk criteria.
- Low-risk patients included patients who had not been hospitalised in hospital A during the outbreak period. These patients were considered not to be exposed to OXA-48 carriers.

Patients were flagged accordingly in the electronic patient record system, which provided automatic pop-ups for OXA-48 carriers, high-risk, and medium-risk patients, in order to allow adequate precautions as

described in the sections 'screening' and 'infection control measures'.

## Screening

### Retrospective screening

Retrospective screening included PCR-based screening of OXA-48 and CTX-M group 1 ESBL of all *K. pneumoniae* isolates that had been stored since 1 January 2009. There was protocolised storage of all clinical isolates from blood cultures (irrespective of antibiotic susceptibility) and of all clinical isolates with an ESBL phenotype, supplemented with isolates with otherwise notable antibiograms. Retrospective screening started mid-May 2011 as the presence of carbapenemases was, based on phenotype, suspected in some clinical *K. pneumoniae* isolates.

### Prospective screening

Prospective screening for Enterobacteriaceae$_{OXA-48}$ included obtaining swabs (Amies Agar Gel 108C, Copan) on three consecutive days from rectum, throat and possible infection sites, such as wounds, sputum, and urine, when applicable. After outbreak notification, hospitalised patients were screened using conventional culture techniques, and high-throughput PCR-based screening for OXA-48 started on 10 June 2011.

- Patients in the high-risk group were screened on readmission when hospitalised, and if not hospitalised through post-discharge screening. For this, non-hospitalised high-risk patients received information and material for sampling that could be returned through mail. High-risk patients were not recalled to the hospital to be screened.
- Patients in the medium-risk group were screened on readmission when hospitalised.
- Patients in the low risk group were not screened on admission.

To detect unnoticed OXA-48 transmission in the hospital, all patients hospitalised for more than seven

**Table 1**

Risk group classification of patients during an outbreak of OXA-48 positive Enterobacteriaceae in a hospital, Rotterdam, the Netherlands, 2009–2011

| Risk group (number in group) | Screened N(%) | OXA-48 positive N(% of screened) | Definition | Identification strategy | Barrier precautions |
|---|---|---|---|---|---|
| OXA-48 carrier (118) | NA | NA | Patients with a clinical culture (taken because of a clinical suspicion of infection by treating physician) or screening culture (taken with the purpose of detecting OXA-48 carriage, without a clinical suspicion of infection) taken after 1 Jan 2009, containing PCR-confirmed OXA-48 positive Enterobacteriaceae, excluding Shewanella spp.<br><br>The status of OXA-48 carrier was maintained unless six consecutive screening cultures from the patient performed every two months were negative (i.e. 1 year negative) | NA | Single room<br><br>Gowns and gloves<br>Masks during high risk interventions |
| High-risk (4,722) | 3,394 (72) | 35 (1) | Shared room with or was in same room within 2 hours after discharge and/or transfer to another room of OXA-48 carrier<br><br>Had Enterobacteriaceae in clinical sample with MIC for imipenem ≥2 mg/L or meropenem ≥0.5 mg/L, or shared room with or was in same room within 2 hours after discharge and/or transfer to another room of such a patient | Screening on readmission when hospitalised<br><br>Post-discharge screening when not hospitalised<br><br>From Jun 2011 to Jan 2012 weekly screening when hospitalised >7 days | Single room[a]<br><br>Gowns and gloves<br>Masks during high risk interventions |
| Medium-risk (67,361) | 4,133 (6) | 8 (<1) | Was admitted to hospital A during outbreak period (1 Jul 2009–18 Jul 2011), and did not fulfil criteria for OXA-48 carrier or high-risk | Screening on readmission when hospitalised<br><br>From Jun 2011 to Jan 2012 weekly screening when hospitalised >7 days | Cohorting[b]<br><br>General precautions |
| Low-risk (ND) | 1,921 (NA) | 4[c] (<1) | Was not admitted to hospital A during outbreak period (1 Jul 2009–18 Jul 2011) | Point-prevalence surveys<br><br>From Jun 2011 to Jan 2012 weekly screening when hospitalised >7 days | Cohorting[b]<br><br>General precautions |

MIC: minimum inhibitory concentration; NA: not applicable; ND: not determined; PCR: polymerase chain reaction.

[a] Single room or cohorting with other high-risk patients, if insufficient availability of single rooms.

[b] Cohorting with patients in the same risk group.

[c] Not epidemiologically linked to outbreak.

days, including low risk patients and high/medium risk patients, were screened weekly from June 2011 onwards (until January 2012).

## Microbiology

### Screening patients and isolates for OXA-48

Screening swabs were inoculated – overnight – in broth containing ertapenem (0.125 mg/L).

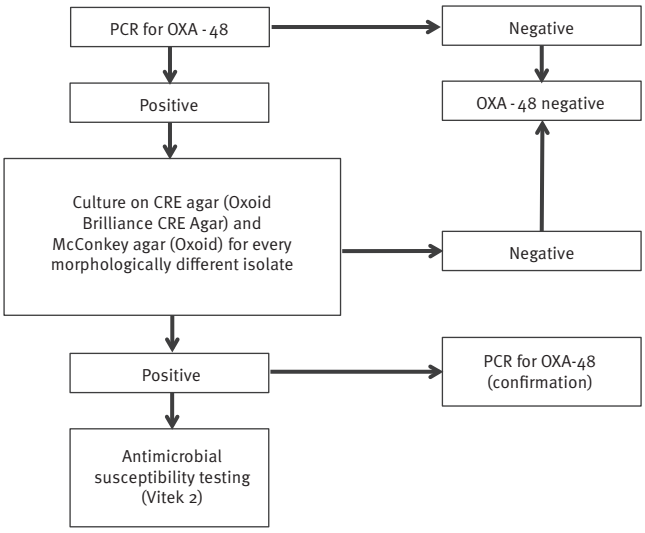
A robotised PCR-procedure was designed using the following primers: OXA-48 Forward 5'-GCGTGGTTAAGGATGAACAC-3', OXA-48 Reverse 5'-CATCAAGTTCAACCCAACCG-3', and OXA-48 probe, labelled with 6-carboxyfluorescein (FAM), 5'-FAM-AGCCATGCTGACCGAAGCCAATG-3', generating a DNA fragment of 438 bp. This PCR was modified from Poirel et al. [19].

In case of PCR positivity, isolates, regardless of the retrospective or prospective sampling procedure, were cultured on carbapenem-resistant Enterobacteriaceae (CRE) agar (Oxoid Brilliance CRE Agar) and McConkey agar (Oxoid), and the presence of OXA-48 was reconfirmed by PCR in every morphologically different isolate, to a maximum of six colonies (Figure 1). Validation of this procedure before large-scale application yielded 100% specificity.

MICs for amikacin, cefepime, cefotaxime, ciprofloxacin, gentamicin, imipenem, meropenem, and trimethoprim/sulfamethoxazole were determined by automated susceptibility testing (Vitek 2) and MIC for ertapenem was determined by Etest (bioMérieux, Marcy l'Etoile, France).

**Figure 1**

Schematic representation of polymerase chain reaction-based screening procedures used during an outbreak of OXA-48 positive Enterobacteriaceae in a hospital, Rotterdam, the Netherlands, 2009–2011




PCR: polymerase chain reaction; CRE: carbapenem-resistant Enterobacteriaceae.

### Screening OXA-48 positive isolates for extended-spectrum beta-lactamases phenotype

For all isolates found to be OXA-48 positive by the method above (Figure 1), ESBL phenotype was verified. ESBL phenotype was defined as a MIC ≥1 mg/L for cefotaxime, or ceftazidime, and confirmation results of disk diffusion using cefepime, cefotaxime, and ceftazidime, with and without clavulanic acid according to national guidelines [20].

### Screening *Klebsiella pneumoniae* isolates with extended-spectrum beta-lactamases for CTX-M group 1

Regardless of whether they were obtained from retrospective of prospective screening, *K. pneumoniae* isolates with ESBL phenotype (only 1st isolate per patient) were tested by PCR for CTX-M group 1 (primers: Forward 5'-GCTGGACTGCCTGCTTCCT-3', Reverse 5'- CGTTGGTGGTGCCATAG(C/T)CA-3', and minor groove binder (MGB) probe 5'-CCGCTGCCGGTCTTATC-MGB-3'), and CTX-M group 1 isolates were sequenced or tested with gene-specific PCR for CTX-M-15.

### Molecular investigation of the outbreak

CTX-M group 1 and/or OXA-48 *K. pneumoniae* isolates were genotyped using amplified fragment length polymorphism (AFLP) [21,22]. Similarity was defined as ≥85% resemblance (Dice). AFLP typing was performed for all *K. pneumoniae* isolates included in retrospective screening, as well as for *K. pneumoniae* isolates detected through prospective screening.

A plasmid multilocus sequence typing (pMLST) scheme was developed for typing of $bla_{OXA-48}$ containing plasmids. Plasmid sequences were filtered from the reported whole genome sequence of the outbreak-related *K. pneumoniae* 1191100241 (Project 71587 GenBank Assignment: AFXHoooooooo). Four contigs were identified and PCR and conventional sequencing enabled the determination of the order and orientation of the contigs as well as the closure of the remaining gaps in the sequence. A basic local alignment search tool (BLAST) search identified four plasmids with a similar backbone: pCTXM360 *K. pneumoniae* (GenBank accession number: EU938349.1); pNDM-HK *E. coli* (GenBank accession number: HQ451074.1); pEL60 *Erwinia amylovora* (GenBank accession number: AY422214.1); pCTX-M3 *C. freundii* (GenBank accession number: AF550415.2). Initial analysis of these plasmids showed 11 potential sequences with sequence variation.

The four sequences with most sequence variation were selected and their usefulness for typing was validated in 13 OXA-48 encoding plasmids: Plasmids from six isolates were from the current outbreak (as was the whole genome sequenced isolate), one isolate was possibly outbreak related, but from a different hospital, and six

isolates were obtained from six different geographic locations in the Netherlands, and considered unrelated to this outbreak. Four of the six plasmids from the isolates unrelated to the outbreak had clear sequence differences compared to the *K. pneumoniae* 1191100241 OXA-48 plasmid, whereas only one of the six plasmids obtained from outbreak-related isolates had clear differences. The plasmid from the isolate that was possibly outbreak related but from a different hospital had a nucleotide difference. From these data we concluded that the chosen sequences provided sufficient resolution.

We did not determine the incompatibility group or performed transfer experiments because the incompatibility class could be deduced from the whole genome sequence data and pMLST is more discriminatory than the determination of the incompatibility group. Isolates for plasmid typing were selected from 15 patients who had at least two different OXA-48 containing Enterobacteriaceae, of which one *K. pneumoniae*, maximising diversity in species.

# Results

## Infection control measures

Prior to the notification of the outbreak of OXA-48 positive Enterobacteriaceae, a certain number of steps had already been taken to contain *K. pneumoniae* with ESBL phenotype, which had been detected in the hospital from 2009 onwards (Table 2). After notification in May 2011 of *K. pneumoniae*CTX-M-15 simultaneously positive for OXA-48, in clinical cultures of two patients who had been recently discharged from hospital A, an outbreak team was assembled on 1 June. PCR procedures for OXA-48 screening were fully operational on 10 June 2011. On 18 July 2011, all infection control measures as described in the 'Infection control' section had been implemented and accurate flagging of all patients in hospital database systems had been realised.

## Screening

### Retrospective screening

The identification of two patients with *K. pneumoniae*-CTX-M-15;OXA-48 by other laboratories in March and April 2011 alerted to the outbreak upon notification on 31 May 2011. These two OXA-48 carriers are included in the group of the retrospectively screened patients in further analyses.

Furthermore, retrospective evaluation of all stored *K. pneumoniae* isolates (n=408) revealed 85 isolates harbouring OXA-48, from 43 patients (Figure 2); 77 isolates were also positive for CTX-M-15. The 'oldest' OXA-48 isolate (also harbouring CTX-M-15) was identified in a clinical sample obtained on 10 September 2010.

### Detection of OXA-48 carriers by prospective hospital screening or clinical sample testing

Accurate flagging of all patients in the hospital database systems as 'low', 'medium' or 'high' risk was realised on 18 July 2011. Between outbreak detection (31 May 2011) and full implementation of the flagging system (18 July 2011) prospective hospital screening or testing of clinical samples revealed OXA-48 carriage in 30 hospitalised patients (Figure 2). The 30 patients detected through prospective screening or clinical samples were different from the 45 patients found by retrospective screening. Two of these 30 patients were

**Table 2**

Control measures for extended-spectrum beta-lactamases (ESBL) and OXA-48 producing Enterobacteriaceae during an outbreak of OXA-48 positive Enterobacteriaceae, Rotterdam, the Netherlands, 2009–2011

| Date | Measure |
|---|---|
| Jun 2010 | - Separation of two ICU-units<br>- Increased attention for hygiene measures<br>- Enhanced cleaning of ICU-units |
| Aug 2010 | Start twice weekly throat and rectum screening for *K. pneumoniae* with ESBL phenotype in ICU patients |
| Sep 2010 | Start making of daily summary of all relevant microorganisms on ICU |
| Oct 2010 | Hand hygiene promotion on ICU |
| Mar 2011 | - Cohorting of patients with ESBL *K. pneumoniae*<br>- Dedicated nursing staff in two ICU-units<br>- Strict isolation[a] for patients with a ESBL-like microorganism on ICU<br>- ICU discharge cultures<br>- Strict isolation[a] for all patients transferred from ICU to ward until ICU discharge cultures are negative<br>- Contact-droplet isolation[b] for non-ICU patients with HRMO |
| May 2011 | Start of SDD in ICU prior to the relocation of the hospital into a new building |
| Jun 2011 | Notification of OXA-48 positive Enterobacteriaceae outbreak. Start PCR based screening for OXA-48 and pre-emptive isolation as described in Table 1 |
| July 2011 | All patients are flagged according to risk categories for $Enterobacteriaceae_{OXA-48}$ carriage or exposure |

ESBL: extended spectrum beta-lactamase; HRMO: highly resistant microorganism; ICU: intensive care unit; PCR: polymerase chain reaction; SDD: selective decontamination of the digestive tract.

[a] Strict isolation: single isolation room, use of gown, gloves and mask.

[b] Contact-droplet isolation: single room, use of gloves and mask.

identified in August, but both had been hospitalised from before 18 July.

In total, 72,147 patients had been admitted during the outbreak period (1 July 2009 until 18 July 2011). By the time flagging of patients was completely operational (18 July 2011), 64 of these patients had already been categorised as OXA-48 carriers. Of the 72,083 remaining, 4,722 were classified as high-risk and 67,361 as medium-risk, of whom 3,394 (72%) and 4,133 (6%) were screened respectively post-discharge or on readmission (Table 1). This yielded 43 newly identified OXA-48 carriers (35 from the high-risk and eight from the medium-risk patient group). The last patient with OXA-48 was detected through post-discharge screening on 14 April 2012.

In all, of 73 OXA-48 carriers detected prospectively, five were detected via clinical cultures while 68 were identified through screening. All 68 had documented rectal carriage and 13 (19%) also had throat carriage.

In total, prospective and retrospective analysis led to 118 OXA-48 carriers being found (Figure 2).

In a period after the outbreak starting from 18 July 2011 until 18 July 2012, 1,921 patients (not admitted between 1 July 2009 up to 17 July 2011 included) were screened for OXA-48 carriage after seven days hospitalisation or during point-prevalence surveys. In this period three patients with OXA-48 Enterobacteriaceae (one *C. freundii*, one *E. coli* and one *K. pneumoniae*) were detected through point-prevalence survey. Another patient had OXA-48 *K. pneumoniae* in a clinical culture obtained at hospital admission. All findings could not be epidemiologically linked to the outbreak and both *K. pneumoniae* isolates did not belong to the outbreak strain based on AFLP-typing. These episodes were, therefore, considered new introductions.

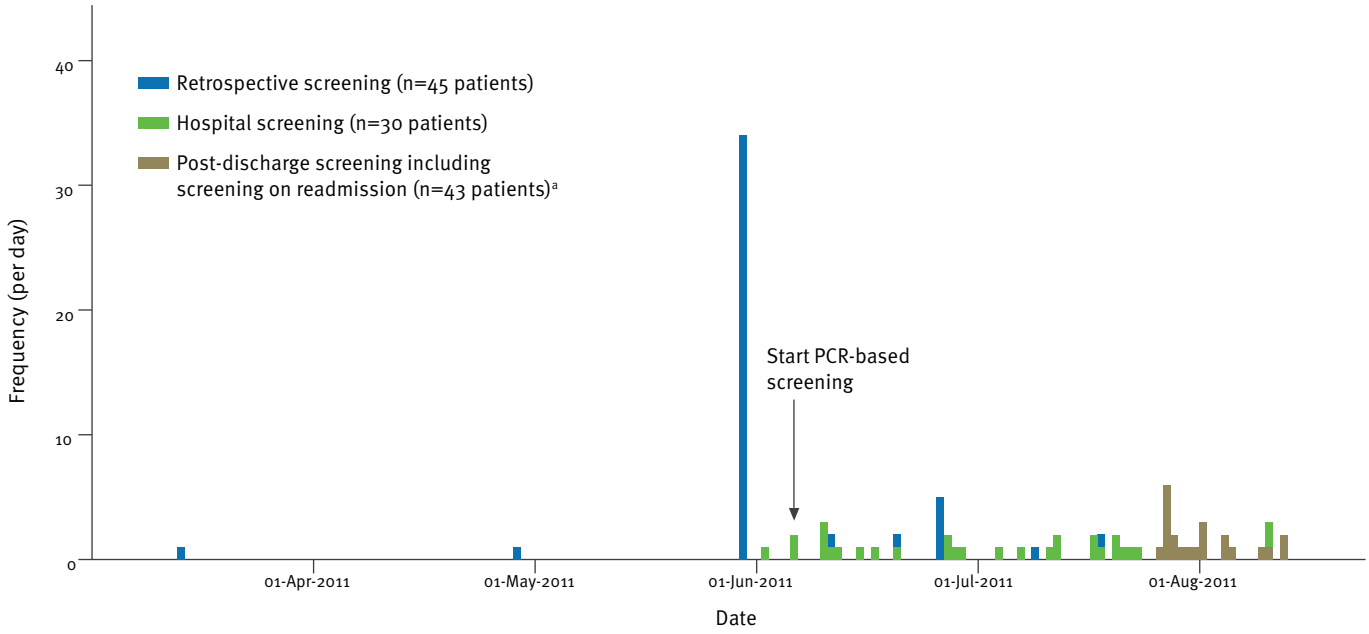
## Patient characteristics

In 21 of 118 patients (18%) Enterobactericeae$_{OXA-48}$ was associated with clinical signs of infection and all-cause 30-day mortality was 29% (n=6) and 13% (n=13) for patients with infection (n=21) and colonisation only (n=97), respectively (Table 3).

Before the transmigration of both hospital locations (16 May 2011), 107 patients with OXA-48 Enterobacteriaceae had been hospitalised and they had a median of seven roommates per admission (interquartile range (IQR): 3–15), which generated a median of 1.04 (IQR: 0.6–3.0) new contact patients per admission day. After transmigration (and before 18 July 2011) 49 OXA-48 carriers were hospitalised with a median of 0 roommates (IQR: 0–4), generating a median of 0 (IQR: 0–1.56) new contacts per admission day (p<0.001).

**Figure 2**

Epidemic curve of detection date of first OXA-48 positive isolate per patient during an outbreak of OXA-48 positive Enterobacteriaceae, Rotterdam, the Netherlands, 2009–2011 (n=118 patients)[a]




PCR: polymerase chain reaction.

The first two patients were detected in March and April 2011, but notified in May 2011, by other laboratories and are included in the retrospective analysis. Before 10 June PCRs were already performed, but the automated PCR was not fully operational until 10 June so this date was considered the start of PCR-based screening. The retrospective detection was performed on stored *Klebsiella pneumoniae* samples dating back to 1 January 2009, with the oldest positive sample for OXA-48 dating back from 10 September 2010.

[a] 21 patients detected after 15 August 2011 are not shown.

## Microbiology and antibiotic susceptibility

In 55 of 118 patients (47%) OXA-48 was detected in more than one Enterobacteriaceae species; patients had five (n=1), four (n=3), three (n=13), or two (n=38) different species. OXA-48 was most frequently identified in *K. pneumoniae* (n=99 patients, 83.9%) and *E. coli* (n=58 patients, 49.2%) (Table 3).

**Table 3**

Characteristics of OXA-48 positive patients during an outbreak of OXA-48 positive Enterobacteriaceae in a hospital, Rotterdam, the Netherlands, 2009–2011 (n=118)

| Characteristics of OXA-48 positive patients | Patients with OXA-48 Enterobacteriaceae (n=118,494 admissions) |
|---|---|
| Sex, n male (%) | 67 (57) |
| Age in years, median (IQR) | 70.6 (60.7–78.0) |
| Median length of stay in days per admission (IQR) | 4 (1–14) |
| Median number of admissions during outbreak period (IQR) | 3 (2–6) |
| Number of patients admitted to ICU during outbreak period (%) | 52 (44) |
| Number of admissions per specialty (%) | |
| Internal medicine | 160 (32) |
| Surgery | 119 (24) |
| Gastro-enterology | 43 (9) |
| Cardiology | 37 (7) |
| Urology | 36 (7) |
| Pulmonology | 27 (5) |
| Other | 72 (15) |
| Combination of OXA-48 positive organisms found, n | |
| Only *Klebsiella pneumoniae* | 51 |
| *K. pneumoniae* and *Escherichia coli* | 25 |
| *K. pneumoniae* and other[a] | 6 |
| *K. pneumoniae* and *E. coli* and other[a] | 17 |
| Only *E. coli* | 9 |
| *E. coli* and other[a] | 7 |
| Only other[a] | 3 |
| Infection with OXA-48 positive Enterobacteriaceae, n (%) | 21 (18) |
| Patients infected by infection site, n (n with positive blood culture) | |
| Urinary | 5 (3) |
| Pulmonary | 9 (5) |
| Abdominal | 5 (5) |
| Vascular | 1 (1) |
| Osteomyelitis | 1 (1) |
| 30 day mortality after first positive isolate, n (%) | 19 (16) |
| Infection: deaths/patients infected (%) | 6/21 (29) |
| Colonisation: deaths/patients colonised (%) | 13/97 (13) |

ICU: intensive care unit; IQR: interquartile range.

[a] Other organisms included *Klebsiella oxytoca* (n=8), *Enterobacter cloacae* (n=7), *Morganella morganii* (n=6), *Citrobacter freundii* (n=3), *Serratia marcescens* (n=3), *Enterobacter aerogenes* (n=2), *Citrobacter braakii*, *Citrobacter farmeri*, *Citrobacter koseri*, *Citrobacter youngae*, *Escherichia fergusonii*, *Klebsiella ozaenae*, *Kluyvera* species and *Raoultella planticola* (all n=1).

Depending on breakpoints used, at least 85% of OXA-48 isolates (*K. pneumoniae* and *E. coli*) were susceptible to meropenem and amikacin (Table 4).

All OXA-48 *K. pneumoniae* isolates with CTX-M group 1 ESBL had CTX-M-15 (n=64). Of these 64 patients, 18 also had *K. pneumoniae*$_{OXA-48}$ isolates (without ESBL), and both isolates were used to describe antibiotic susceptibility (Table 4).

In *K. pneumoniae* the combination of OXA-48 and CTX-M-15 was associated with resistance to cefepime, cefotaxime, and gentamicin. Using various Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, susceptibility to imipenem of *K. pneumoniae*OXA-48 isolates (without ESBL) ranged from 12% (CLSI 2010 updated breakpoints [23]) to 83% (CLSI 2006 breakpoints [24]) and ranged from 3% to 72%, respectively, for *K. pneumoniae*O$_{XA-48;CTX-M-15}$. All *K. pneumoniae*$_{OXA-48}$ isolates tested (n=108) were non-susceptible to ertapenem (MIC ›0.25 mg/L), as were 45 of 49 *E. coli* (Table 4).

## Molecular epidemiology of *Klebsiella pneumoniae*

285 *K. pneumoniae* isolates from patients admitted during the outbreak were included for analysis; 62 OXA-48/CTX-M-1 group, 158 CTX-M-1 group (without OXA-48), 49 with OXA-48 (without CTX-M-1 group ESBL) and 16 with non-CTX-M-1 group ESBL. Of these, 203 isolates were considered to be clonally linked; 62 OXA-48/CTX-M-15, 107 CTX-M-1 group (without OXA-48) and 34 with OXA-48 (without CTX-M-1 group ESBL) (Figure 3 and 4).

Among the 82 non-outbreak type *K. pneumoniae* isolates, 50 different types were detected, yielding one cluster of seven isolates (OXA-48 negative, CTX-M-1 group positive (n=5), OXA-48 negative, non-CTX-M-1 group ESBL (n=2)), one of five (all OXA-48 negative, CTX-M-1 group positive), six of three (4 clusters OXA-48 negative, CTX-M-1 group positive; 1 cluster with OXA-48 negative non-CTX-M-1 group or CTX-M-1 group ESBL positive; and 1 cluster with 2 OXA-48 positive ESBL negative and 1 OXA-48 negative non-CTX-M-1 group ESBL positive), 10 of two isolates and 32 unique isolates. There were no clusters with more than two OXA-48 positive isolates among the non-outbreak isolates.

From September 2010 onwards clonal types *K. pneumoniae*$_{OXA-48;CTX-M-15}$ were identified, followed by an increase in clonal types with OXA-48 but without CTX-M-15 in June 2011. These findings are compatible with cross-transmission of clonal *K. pneumoniae* with considerable heterogeneity in the presence of OXA-48 and CTX-M-15. OXA-48 encoding plasmids from 39 of 41 isolates (95%) belonging to 13 different species obtained during the outbreak from 15 patients were identical (based on pMLST), suggesting inter-species transmission of plasmids.

## Table 4

Susceptibility of first OXA-48 positive ESBL positive and negative isolate per patient per organism as determined by Vitek 2 during an outbreak of OXA-48 positive Enterobacteriaceae, Rotterdam, the Netherlands, 2009–2011 (n=118 patients, 171 isolates)

| Antibiotic | Breakpoint[a] (mg/L) | *K. pneumoniae* OXA-48, no ESBL (n=52) | | *K. pneumoniae* OXA-48 and CTX-M-15 (n=64) | | *E. coli* OXA-48, no ESBL (n=49) | | *E. coli* OXA-48 and CTX-M-15 (n=6) | |
|---|---|---|---|---|---|---|---|---|---|
| | | $MIC_{90}$ | S, n (%) | $MIC_{90}$ | S, n (%) | $MIC_{90}$ | S, n (%) | $MIC_{90}$ | S, n (%) |
| Meropenem | | 2 | | ≥16 | | 1 | | 1 | |
| Breakpoint CLSI 2010-U | 1 | – | 44 (85) | – | 47 (73) | – | 49 (100) | – | 6 (100) |
| Breakpoint EUCAST | 2 | – | 49 (94) | – | 49 (77) | – | 49 (100) | – | 6 (100) |
| Breakpoint CLSI 2006 | 4 | – | 49 (94) | – | 49 (77) | – | 49 (100) | – | 6 (100) |
| Imipenem | | 8 | | ≥16 | | 2 | | 4 | |
| Breakpoint CLSI 2010-U | 1 | – | 6 (12) | – | 2 (3) | – | 35 (71) | – | 1 (17) |
| Breakpoint EUCAST | 2 | – | 18 (35) | – | 15 (23) | – | 46 (94) | – | 3 (50) |
| Breakpoint CLSI 2006 | 4 | – | 43 (83) | – | 46 (72) | – | 47 (96) | – | 6 (100) |
| Ertapenem | 0.25[b] | 32 | 0 (0)[c] | ≥32 | 0 (0)[d] | 2 | 4 (8)[e] | 2 | 0 (0)[f] |
| Amikacin | 8 | ≤2 | 51 (98) | 8 | 61 (95) | ≤2 | 47 (96) | 16 | 5 (83) |
| Ciprofloxacin | 0.5 | ≥4 | 16 (31) | ≥4 | 0 (0) | ≥4 | 42 (86) | ≥4 | 1 (17) |
| Trimethoprim/ sulfamethoxazole | 2 | ≥16 | 14 (27) | ≥16 | 0 (0) | ≥16 | 43 (88) | ≥16 | 1 (17) |
| Gentamicin | 2 | ≥16 | 45 (87) | ≥16 | 0 (0) | 8 | 44 (90) | ≥16 | 4 (67) |
| Cefotaxime = ceftriaxon | 1 | ≤1 | 47 (90) | ≥64 | 0 (0) | 2 | 44 (90) | ≥64 | 0 (0) |
| Cefepime | 1 | ≤1 | 52 (100) | ≥64 | 0 (0) | ≤1 | 49 (100) | 32 | 3 (50) |

CLSI: Clinical and Laboratory Standards Institute; *E. coli*: *Escherichia coli*; ESBL: extended-spectrum beta-lactamases; EUCAST: European committee on antimicrobial susceptibility testing; *K. pneumoniae*: *Klebsiella pneumoniae*; MIC: minimum inhibitory concentration; S: susceptible.

[a] Susceptibility according to EUCAST-breakpoints unless otherwise specified.

[b] Screening breakpoint.

[c] Only 49 of the total 52 *K. pneumoniae* OXA-48, no ESBL were tested for ertapenem.

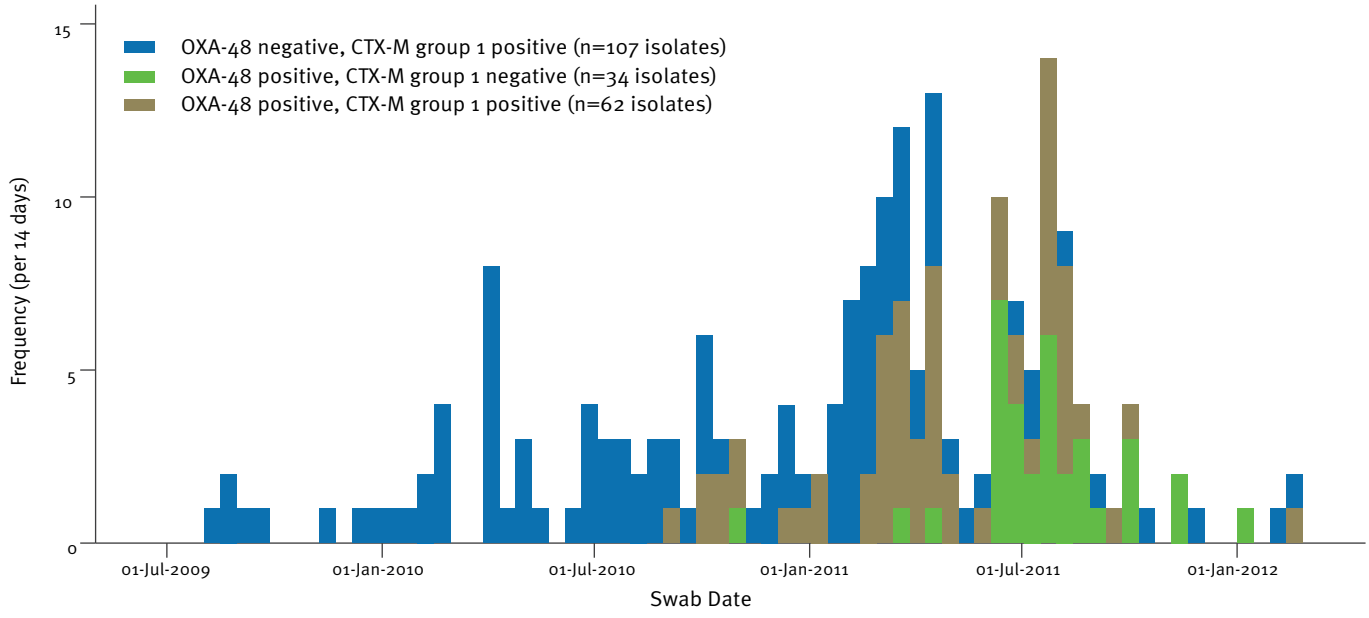
[d] Only 59 of the total 64 *K. pneumoniae* OXA-48 and CTX-M-15 isolates were tested for ertapenem.

[e] Only 44 of the total 49 *E. coli* OXA-48, no ESBL isolates were tested for ertapenem.

[f] Only five of the total six *E. coli* OXA-48 and CTX-M-15 isolates were tested for ertapenem.

## Figure 4

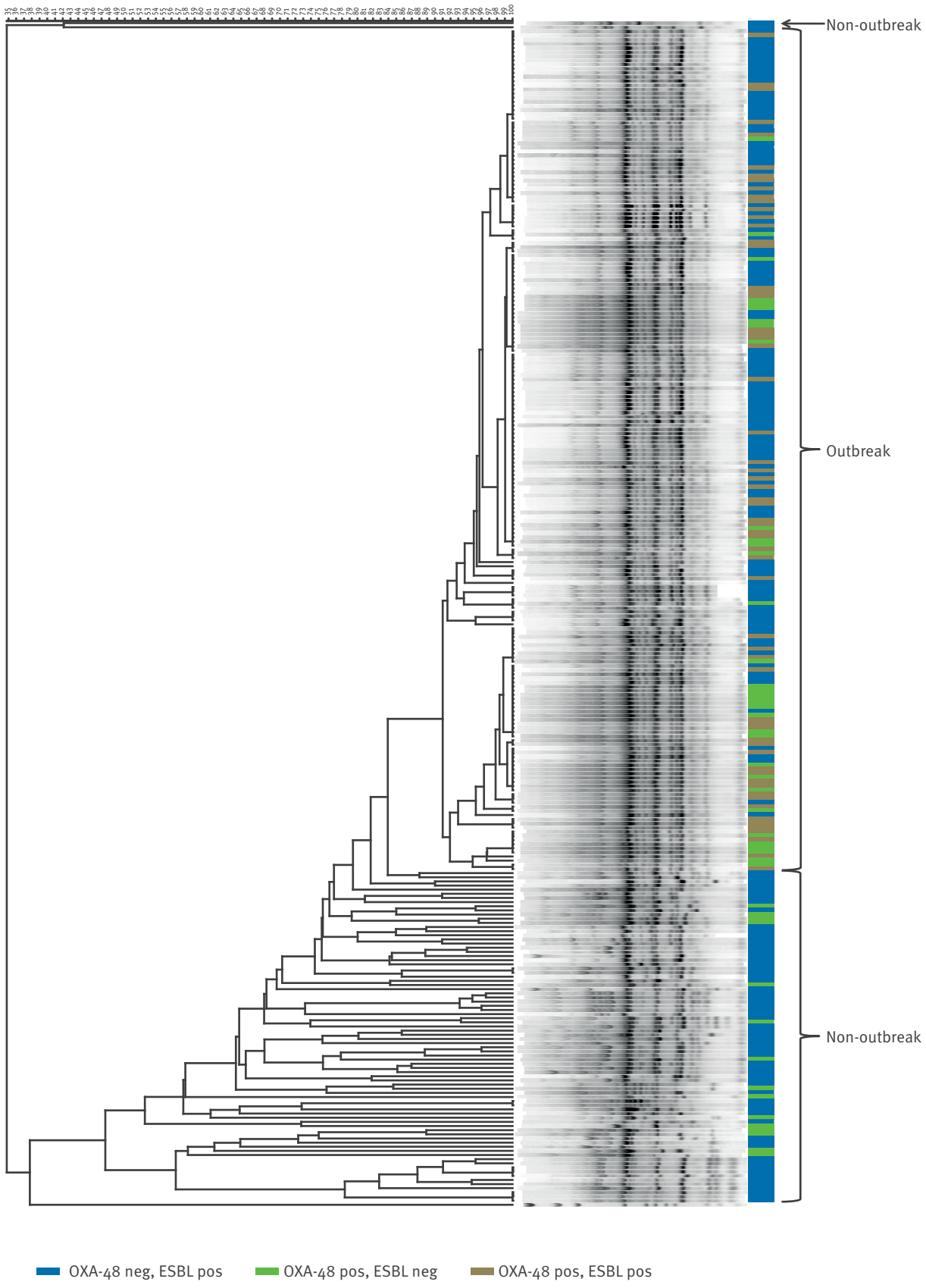
Epidemic curve of outbreak strain *Klebsiella pneumoniae* isolates producing extended-spectrum beta-lactamases (ESBL) and/or OXA-48, Rotterdam, the Netherlands, 2009–2012 (n=203 isolates)




Isolates included in the Figure, detected after 18 July 2011, are from patients admitted during the outbreak period, but screened after the outbreak period in post-discharge and re-admission screening.

## Figure 3

AFLP-typing of 285 *Klebsiella pneumoniae* isolates, during an outbreak of OXA-48 positive Enterobacteriaceae, Rotterdam, the Netherlands, 2009–2012




AFLP: amplified fragment length polymorphism; ESBL: extended-spectrum beta-lactamases; neg: negative; pos: positive.

Outbreak isolates are based on ≥85% similarity of AFLP patterns (Dice).

One *K. pneumoniae* outbreak isolate was sequenced and categorised as ST395, and 147 isolates also underwent pulsed-field gel electrophoresis (PFGE) typing, yielding comparable results to AFLP typing (with regard to classification as outbreak-related or not) for 143 isolates (data not shown).

## Discussion

We describe here the successful control of a large hospital outbreak of OXA-48 producing Enterobacteriaceae, which started with nosocomial transmission of *K. pneumoniae*$_{CTX\text{-}M\text{-}15}$ that apparently acquired OXA-48. Among outbreak strains, there was considerable inter- and intra-species heterogeneity in antibiotic susceptibility and resistance genes, and circumstantial evidence of cross-species transfer of OXA-48 containing plasmids. Before the hospital-wide implementation of classical infection control measures and large-scaled PCR-based screening for carriage with OXA-48 containing bacteria, as described here, the outbreak had persisted, partly unnoticed and insufficiently controlled, for two years.

In absence of other resistance genes, OXA-48 expression usually results in low-level resistance, which may hamper laboratory detection. Co-production of ESBL and changes in permeability and in efflux pumps are usually needed for higher resistance levels [2]. In this hospital CLSI 2006 breakpoints were used during the outbreak period, which implied that MICs for imipenem and meropenem ≤4 mg/L were considered susceptible. Although the susceptibility breakpoint for both antibiotics had been reduced to MIC ≤1 mg/L by CLSI in 2010, even at these new breakpoints 78% (91/116) and 7% (8/116) of *K. pneumoniae*$_{OXA\text{-}48}$, and 100% (55/55) and 65% (36/55) of *E. coli*$_{OXA\text{-}48}$ isolates would have been considered susceptible to meropenem and imipenem, respectively. Based on EUCAST guidelines 84% (98/116) and 28% (33/116) of *K. pneumoniae*$_{OXA\text{-}48}$, and 100% (55/55) and 89% (49/55) of *E. coli*$_{OXA\text{-}48}$ isolates would have been considered susceptible to meropenem and imipenem, respectively. Ertapenem susceptibility testing (using the screening breakpoint of >0.25 mg/L) would have detected 128 of the 132 OXA-48 isolates (97%) with meropenem MIC ≤1 mg/L, and is, therefore, the carbapenem of choice when screening for OXA-48. This phenotypic variability among OXA-48 containing bacteria represents a major threat for unnoticed spread of this resistance gene. Large-scale gene detection, routine testing for ertapenem susceptibility, or novel phenotypic methods (such as chromogenic media) may be needed to prevent unnoticed dissemination. The latter methods however, yield considerable variation in sensitivity for OXA-48 detection, with 84% for carbapenem-resistant Enterobacteriaceae (CRE) agar [25] and 100% for the Carbapenemase Nordmann-Poirel (Carba NP) test [26].

As with most hospital outbreaks, the simultaneous implementation of interventions and lack of quantitative evaluation of adherence to these interventions precludes a truly scientific analysis of their effectiveness. Our findings suggest that contact isolation measures using single rooms with individual sanitary facilities attributed to controlling transmission. This was feasible as two old hospital buildings had transmigrated to a new building with more single rooms, shortly before outbreak detection. Naturally this migration might have influenced infection control also in other ways, such through differences in building structure that could not be quantified. Furthermore, widespread knowledge of an ongoing outbreak (with significant attention by the lay press) since June 2011 may also have contributed to better adherence to basic infection control measures. Based on the data available there was no evidence of environmental contamination or carriage among healthcare personnel with the outbreak strain.

The largest proportion of patients had been treated in ICU, suggesting that this was the epicentre of the outbreak. Yet, detection bias due to higher culture frequency is likely. Moreover, most identification was based on either retrospective or post-discharge screening and many patients had been treated in different wards. Therefore, more sophisticated analyses are needed to determine the relative importance of different wards in the outbreak.

Selective decontamination of the digestive tract (SDD) has been associated with eradication (or suppression) of resistant Gram-negative bacteria in the gut [27-29]. SDD (using tobramycin and polymyxin E) was introduced in the ICU in hospital A in May 2011, just before the transition to the new facility and hospital-wide implementation of control measures. SDD was not intended to eliminate OXA-48 carriage, but was implemented for all eligible patients because of its presumed benefits on patient outcome [30]. Because of the timing of events it will be difficult to quantify the role of SDD in controlling this outbreak. Preliminary analyses do not identify an immediate change in the numbers of hospitalised OXA-48 carriers (data not shown).

The first detected OXA-48 isolate originated from September 2010, but it cannot be excluded that OXA-48 was already present in the hospital before that date. Although many isolates with an ESBL phenotype had been stored, isolates with minimally elevated MICs for carbapenems were not. Furthermore, screening for ESBL-carriage was implemented in ICU in June 2010 and in other departments in August 2010, and hospital-wide PCR-based screening for OXA-48 carriage started in June 2011. In addition, OXA-48 carriers may lose their carrier status which will reduce detection in post-discharge screening. Therefore, underreporting of OXA-48 carriage is likely. Yet, we do not assume OXA-48 was circulating for many years in the hospital. The oldest OXA-48 isolate originated from a culture obtained in September 2010, and more than 40 isolates clonally linked to the outbreak strain (Figure 3) were detected before, but none of them harboured OXA-48.

This strongly suggests widespread circulation of the ESBL-producing strain without OXA-48 in the hospital before September 2010. Indeed, our hypothesis is that the ESBL-producing outbreak strain was circulating in the hospital and acquired the OXA-48-containing plasmid from another patient, most probably coming from an endemic region. Risk factors for OXA-48 acquisition, duration of carriage of OXA-48 after hospital discharge and its transmissibility in the community setting are currently investigated.

In the early phases of outbreak containment several important decisions had to be made, in the absence of scientific evidence. The tentative start of nosocomial OXA-48 transmission needed to be defined on incomplete data. Therefore, a 14-month margin after the 'oldest' isolate, which was identified at the end of May 2011, was taken. Furthermore, it was known that *Shewanella spp.* can carry OXA-48. Yet, the outbreak was considered to be caused by *K. pneumoniae* only. As we detected patients with non-*Klebsiella* Enterobacteriaceae carrying OXA-48 after implementing PCR-based screening of rectal swabs, it was subsequently decided to include Enterobacteriaceae (but not *Shewanella spp.*) in our case definition. Risk categorisation was based on proximity of patients to identified OXA-48 carriers. For feasibility reasons we decided to base this risk on 'room sharing' only, although there are many more potential risk factors. Finally, based on limited data it was decided not to further investigate a potential role of colonised healthcare workers in this outbreak, nor to change environmental cleaning procedures and antibiotic policies. Enforced cleaning and antimicrobial stewardship were considered instrumental in controlling a large OXA-48 outbreak in Spain [31]. In our setting, there were no documented events of nosocomial transmission of OXA-48 Enterobacteriaceae after 18 July 2011 without these measures. We have not performed a detailed analysis of antibiotic use, but in the cohort of patients who were admitted during the outbreak period and who were tested for OXA-48 carriage (and considered non-carrier based on test results; n=11,386) carbapenem use was 0.67 days per 100 admission days. Unfortunately, days in ICU could not be included in this analysis.

After outbreak detection other healthcare facilities in the region were immediately informed and advised to screen patients who had been admitted to hospital A during the outbreak period. Some hospitals also isolated such patients awaiting culture results. To the best of our knowledge, there were no additional carriers identified through screening in other hospitals. There was one secondary case of OXA-48 carriage in a long-term care facility that had received an OXA-48 carrier after treatment in hospital A. Extensive screening failed to identify further spread.

Some important lessons can be learned from this outbreak. First, uncontrolled spread of ESBL-producing bacteria, even at relatively low levels, can turn into an outbreak of carbapenemase-producing bacteria, most probably after horizontal gene transfer. The likelihood of horizontal gene transfer will increase if admission rates of patients with unidentified carriage with such bacteria increases. Currently, this rate appears to be low in the Netherlands and Belgium. In this hospital four new OXA-48 carriers, unrelated to the outbreak, were discovered due to extensive screening of 1,921 patients. In Belgium, eight OXA-48 positive isolates were detected among 4,564 Enterobacteriaceae isolates (one isolate per patient) [32]. Second, because of the large heterogeneity of antibiotic susceptibilities routine phenotypic detection tests may be insufficient for identification of all isolates involved in an outbreak. Third, once detected, this large outbreak could be controlled – in short time – presumably with classical infection control measures, although it was impossible to quantify the contribution of individual measures and the role of special circumstances, such as the relocation of the hospital into a new facility. Because the outbreak might have remained unnoticed for some time however, the resources needed to identify its extent, as well as to screen potential carriers of OXA-48 Enterobacteriaceae were extensive (74,884 PCRs were performed for OXA-48 screening in 2011 and 2012). We, therefore, recommend implementing risk-stratified screening for carriage of these highly resistant bacteria, followed by barrier precautions for carriers detected, in order to prevent the need of costly control measures after detection of an unnoticed outbreak. Risk factor analyses for OXA-48 carriage are, therefore, warranted.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## Conflict of interest

None declared.

## Authors' contributions

The investigators were responsible for data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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# Tuberculosis control in big cities and urban risk groups in the European Union: a consensus statement

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**In low-incidence countries in the European Union (EU), tuberculosis (TB) is concentrated in big cities, especially among certain urban high-risk groups including immigrants from TB high-incidence countries, homeless people, and those with a history of drug and alcohol misuse. Elimination of TB in European big cities requires control measures focused on multiple layers of the urban population. The particular complexities of major EU metropolises, for example high population density and social structure, create specific opportunities for transmission, but also enable targeted TB control interventions, not efficient in the general population, to be effective or cost effective. Lessons can be learnt from across the EU and this consensus statement on TB control in big cities and urban risk groups was prepared by a working group representing various EU big cities, brought together on the initiative of the European Centre for Disease Prevention and Control. The consensus statement describes general and specific social, educational, operational, organisational, legal and monitoring TB control interventions in EU big cities, as well as providing recommendations for big city TB control, based upon a conceptual TB transmission and control model.**

*The city can have as much reduction of preventable disease as it wishes to pay for. Public health is purchasable; within certain natural limitations a city can determine its own death rate.*
*Hermann Biggs, New York City Board of Health, Annual Report, 1915*

## Background

In low-incidence settings, which include most countries in the European Union (EU), tuberculosis (TB) is concentrated in big cities [1]. TB disproportionally affects certain, often overlapping, urban groups such as immigrants from TB high-incidence countries, homeless people, those with a history of drug and alcohol misuse, and people with a history of imprisonment [2–11]. Prevention and control of TB among these risk groups can be hampered by delayed diagnosis, onward transmission and poor treatment adherence [12–16]. For effective TB control, services in EU big cities should be acceptable, accessible, adequate, appropriate and geared towards the needs of urban risk groups. In the last decade, innovative TB control activities in EU big cities have been reported, including mobile digital chest X-ray screening [16–19], the employment of community health workers and peer-educators [20,21], the use of mobile telephone-assisted or video-observed medication monitoring systems [22,23], and the application of molecular epidemiology [24–27]. Systematic implementation of evidence-based and innovative approaches to improve early case finding, case holding and treatment completion in urban risk groups is urgently needed. Exchange of experience from different urban TB programmes in the EU will be key to achieving European TB control.

In February 2008, the European Centre for Disease Prevention and Control (ECDC) published the *Framework Action Plan to fight tuberculosis in the European Union*,

providing proposals on what needed to be done in EU Member States to decrease the burden of TB [28]. The report recognises the concentration of TB in hard-to-find and hard-to-reach populations as one of the major challenges to TB control efforts across the EU and a key strategic element to reduce and eliminate TB. The EU action plan provides an opportunity to re-think urban TB control, specifically among vulnerable populations in the EU, and strengthen work through the exchange of experience, collaborative research, advocacy and cooperation. In this statement, we have summarised key evidence-based and expert opinion-led recommendations to inform the control of TB in big EU cities. For each recommendation, we have provided a brief background and a summary of the evidence available.

## Methods

Informal contacts have existed between some big cities in the EU for over a decade. In October 2005, the Municipality of Paris organised a conference on metropolitan TB in Europe and the theme of TB in big cities was discussed at the 5th European TB conference of the International Union Against Tuberculosis and Lung Disease (The Union) in Dubrovnik in 2009 [29]. During the Wolfheze Conference in 2010 [30], TB control in big cities in Europe featured in the programme for the first time and as a result of this meeting ECDC agreed to facilitate a workshop on urban TB control in December 2010. TB programme managers and TB control physicians from 10 big cities in eight EU countries attended the event in Stockholm and a working group gradually developed and generated this consensus statement on TB control in big cities and urban risk groups in the EU. The preliminary outcomes of a survey on the epidemiology of TB in big cities in the EU, as well as the process and the progress of the working group, were presented at the 2011 Wolfheze conference.

This consensus statement is based upon a conceptual model of structural and intermediate determinants (explained in the next section) of TB exposure, infection, disease and treatment [31], as well as interventions for TB control, especially in urban risk populations (Figure 1). Each section begins with a discussion of the background of general interventions and specific elements for TB control in big cities, and is then followed by agreed recommendations to achieve control of TB in EU cities. These recommendations are rated in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) grading system (Table 1) [32]. Rating was perfomed by one of the authors (RWA) and subsequently ratified by the expert group Detailed information (checklists and critical appraisals) of the SIGN grading process is available on request from the corresponding author. The literature was selected by authors of the consensus statement in a non-systematic search. SIGN grading was developed for the assessment of evidence in clinical studies and is not necessarily directly applicable to all public health interventions. Therefore a risk–benefit, feasibility, cost-effectiveness and value–acceptability assessment of the recommendations has been added in addition to the SIGN grading (Table 2). Due to differences in the ratio of urban and national TB notification rates in EU Member States, this statement has concentrated on urban TB and control in low-incidence (<20 TB notifications/100,000 population) EU countries according to ECDC definition [33]. Although there is a great deal of relevant literature on urban TB and control outside the EU (especially in North America), for the purpose of this consensus statement the working group has focused on European publications when available.

## Social determinants and interventions

### General background

Social determinants, including structural (e.g. social, political, cultural and economic, health system) or intermediary (e.g. crowded living conditions) and the value of equity are major factors that influence health outcomes [34]. Wealth, health and infection inequalities that influence TB morbidity and mortality rates exist in and between EU countries [35–38], and are probably affected by economic crises [39].

### Social determinants and big cities

Social determinants of TB are not exclusive to big cities but urbanisation and the associated poverty and overcrowding that is more commonly found in these locations, impact on the levels of TB [40]. In many big cities outside and inside the EU, socio-economically disadvantaged populations are more prevalent. This is putting all residents at greater risk of TB acquisition but is particularly increasing the risk among certain urban subpopulations [2, 41–43]. Immigrants, legal or undocumented, form a substantial proportion of big city populations in the EU and can contribute considerably to TB incidence [24,42]. Household overcrowding is often found in urban areas and is related to TB incidence [42,44]. Specific urban overcrowding has been described well in shelters for homeless people or facilities for people with drug misuse; two socially excluded groups that are often over-represented in EU big cities [7,18,19,24]. Social determinants are fundamental causes of TB in EU big cities and therefore solutions to control TB must tackle these issues [45]. A social outreach model of care has been advocated [46], including the role of a link worker who can enable integrated health and social care, by, for example, resolving issues related to health, housing need, welfare benefits and immigration, as well as clinical management issues [47].

### Recommendations

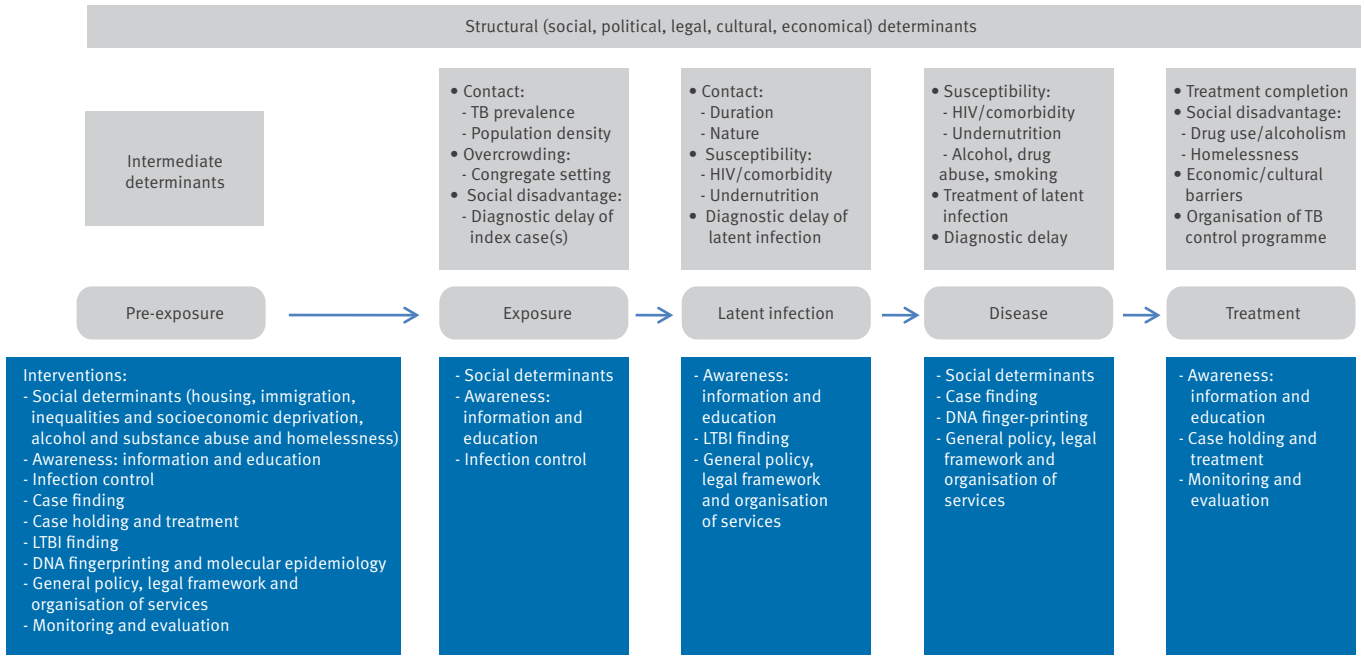
Big city TB control programmes should:

1.1. advocate for sustained political commitment to emphasise the social determinants of health that put subgroups of the population at increased risk of TB;

1.2. investigate and monitor inequalities and socio-economic deprivation and their links with TB in

## Figure

Conceptual model of structural and intermediate determinants of tuberculosis and areas of possible interventions, based on the natural history of tuberculosis from exposure through to infection and disease and treatment




TB: tuberculosis; HIV: human immunodeficiency virus; LTBI: latent tuberculosis infection.

## Table 1

Rating levels of the evidence used to make recommendations to inform tuberculosis control in big cities in the European Union, made in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) grading system

| Rating | Study design | Special conditions | Level of evidence |
|---|---|---|---|
| 1++ | High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias | If directly applicable to target population | A |
| 1+ | Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias | If directly applicable to target population and overall consistency of results | |
| 1++ or 1+ | | Extrapolated evidence | B |
| 2++ | High quality systematic reviews of case control or cohort or studies | If directly applicable to target population and overall consistency of results | |
| | High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal | Extrapolated evidence | C |
| 2+ | Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal | If directly applicable to target population and overall consistency of results | |
| | | Extrapolated evidence | D |
| 3 | Non-analytic studies, e.g. case reports, case series | | |
| 4 | Expert opinion | | |
| 1- | Meta-analyses, systematic reviews, or RCTs **with a high risk of bias** | | No supporting evidence |
| 2- | Case control or cohort studies **with a high risk of confounding or bias and a significant risk that the relationship is not causal** | | |

RCT: Randomised controlled trial

## Table 2

Assessment of the recommendations to inform tuberculosis control in big cities in the European Union, by evidence grading, risk–benefit, feasibility, cost-effectiveness and value–acceptability

| Recommendations | Evidence grading | Risk–benefit | Feasibility | Cost-effectiveness | Value–acceptability |
|---|---|---|---|---|---|
| Recommendation 1.1 | D | Low/high | Possible | Unknown | Unknown/unknown |
| Recommendation 1.2 | D | Low/high | Feasible | Unknown | Unknown/unknown[a] |
| Recommendation 1.3 | D | Low/high | Possible | Unknown | Unknown/unknown[a] |
| Recommendation 1.4 | D | Low/high | Possible | Unknown | Unknown/unknown[a] |
| Recommendation 1.5 | D | Low/high | Possible | Unknown | Unknown/unknown[a] |
| Recommendation 2.1.1 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 2.1.2 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 2.1.3 | B | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 2.2 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 3.1 | D | Low/high | Possible | Unknown | Justified/acceptable[b] |
| Recommendation 4.1 | C | Low/high | Feasible | Possible | Valued/acceptable |
| Recommendation 4.2 | D | Low/high | Feasible | Yes[c] | Unknown/acceptable[d] |
| Recommendation 4.3 | C | Low/high | Feasible | Yes | Valued/acceptable |
| Recommendation 4.4 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 5.1 | D | Low/high | Unknown | Unknown | Unknown |
| Recommendation 5.2 | D | Low/high | Feasible | Unknown | Valued/acceptable[e] |
| Recommendation 5.3 | D | Low/high | Unknown | Unknown | Unknown |
| Recommendation 5.4 | D | Low/high | Unknown | Unknown | Unknown |
| Recommendation 5.5 | D | Low/high | Unknown | Unknown | Unknown |
| Recommendation 6.1 | D | Medium[f]/high[g] | Unknown | Yes[h] | Valued/acceptable[i] |
| Recommendation 6.2 | D | Medium[f]/high[g] | Unknown | Yes[h] | Unknown |
| Recommendation 6.3 | D | Medium[f]/high[g] | Unknown | Yes[h] | Valued/acceptable |
| Recommendation 7.1 | D | Low/high | Feasible[j] | Unknown | Valued/acceptable |
| Recommendation 8.1 | D | Low/high | Possible | Unknown | Unknown/unknown |
| Recommendation 8.2 | D | Low/high | Possible | Unknown | Valued/acceptable |
| Recommendation 8.3 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 8.4 | D | Low/high | Possible | Unknown | Valued/acceptable |
| Recommendation 8.5 | D | Medium[6]/high[7] | Possible | Unknown | Questioned/questioned |
| Recommendation 8.6 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 9.1 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 9.2 | D | Low/high | Feasible | Unknown | Valued/acceptable |
| Recommendation 9.3 | D | Low/unknown | Possible | Unknown | Valued/acceptable |

[a] Acceptability of high cost interventions without clear immediate cost savings but with high cost savings in the future may be difficult in time of economic crisis and austerity.

[b] With education and information.

[c] For latent TB infection screening, not for radiographic screening for disease.

[d] Legal framework may be needed.

[e] Value and acceptability will vary between urban TB risk groups.

[f] Possible hepatotoxic and other adverse effects.

[g] High for the individual; unclear for public health.

[h] For immigrants.

[i] Unclear for preventive treatment.

[j] Cost can be prohibitive.

order to intervene with a comprehensive public health approach [28,37,38];

1.3. collaborate to promote suitable housing for homeless people in order to prevent transmission of TB and promote cure in this population [48-51];

1.4. provide access to social support for all vulnerable populations, irrespective of their status [52-54];

1.5. identify barriers and promote access to healthcare services for all those at risk of TB [21].

## Awareness: information and education interventions

### General background

Targeted provision of information to raise awareness among high-risk groups, in the form of leaflets or through the Internet, has been used for diseases other than TB, such as diabetes, HIV or breast cancer [55,56]. There is an increased drive to use raising awareness as a measure for TB control and to improve knowledge of TB among high-risk groups and the staff who work with them [57].

### Awareness and big cities

Initiatives for raising awareness, such as active information and education strategies, should target urban TB risk groups, those working with urban TB risk groups, and healthcare professionals in urban areas [11,23]. To avoid stigmatisation, awareness of TB in risk groups in big cities can be improved on an opportunistic basis, for example, when a patient comes into contact with healthcare services for consultation or screening [11,58–61]. There is evidence from an educational intervention in London that promotion of screening in primary care can improve early identification of both active TB and latent TB infection (LTBI) [58].

### Recommendations

Big city TB control programmes should:

2.1. implement a coordinated programme of education and training to raise and sustain awareness among affected risk groups and communities [11], front-line professionals working with high-risk groups [11,21], and health and social care professionals, such as general practitioners [11,58,62];

2.2. involve affected communities in the design and delivery of training and awareness raising programmes, taking into account cultural, language and literacy issues [11].

## Infection control in community settings

### General background

Infection control (IC) is an essential component of TB control and prevention and is included in the EU Standards of TB Care [63]. Shortcomings in IC have been major contributors to nosocomial outbreaks, including outbreaks in European TB reference centres [64]. Poor ventilation and overcrowding have been drivers of TB transmission in congregate settings such as homeless shelters, prisons and safe drug consumption facilities. General IC principles for healthcare settings can benefit these specific congregate venues [65]. New interest in IC has been awakened by the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB [66].

### Infection control in community settings and big cities

Nosocomial transmission of TB in urban hospitals [67,68], and effective IC measures in these healthcare settings [69], have been described in the EU. Transmission in hostels and shelters attended by risk groups, and prisons in big cities in the EU, have been suggested by conventional epidemiological studies [70] and strong evidence is supplied by molecular epidemiological studies using DNA fingerprint cluster analysis [13,16,19,71–75]. Congregate settings in big cities in the EU can implement hygienic measures (proper room ventilation and illumination, no overcrowding, cough hygiene) and organise TB awareness-raising activities. They can also implement administrative control activities (early guided referral of residents suspected of having TB for diagnosis and isolation), and motivate residents to participate in contact tracing or radiographic screening [16,17,19]. IC can also prevent TB infection or disease among healthcare workers and social workers in big cities [13,65].

### Recommendations

Big city TB control programmes should:

3.1. ensure implementation of IC measures in congregate settings used by urban high-risk groups (in addition to healthcare settings); these should follow national or international best practice guidelines [63].

## Case finding

### General background

TB control depends on early case finding and successful treatment [28]. Active case finding aims to identify those with TB who have not presented themselves to the healthcare system of their own accord, in order to reduce TB transmission [76]. Active case finding can be performed through symptom screening, questionnaire-based screening (including risk factors), radiographic (e.g. chest X-ray) screening, sputum examination (e.g. microscopy, culture or rapid molecular techniques, including automated nucleic acid amplification tests). Reviews of contact tracing and immigrant screening in the EU [77,78], and effectiveness and cost-effectiveness of TB screening, have been published recently [10]. Disparities in active case finding in the EU have been described [79].

### Case finding and big cities

The assumption that urban TB risk groups will present promptly, complete a diagnostic process that is sometimes difficult and prolonged, and take treatment lasting a minimum of six months is not a basis for effective TB control [45]. Active case finding among urban

high-risk groups should be complemented by tailored strategies for completion of the diagnostic process and treatment. These strategies include low-threshold public health TB 'one-stop shops' with sufficient nursing, social and community healthcare worker staff, appropriate outpatient clinical follow-up or the ability to admit patients to general hospitals or modern-day sanatoria (also called tertiary TB treatment centres). Policies should be backed up by adequate legal frameworks for social support and protection and ensure knowledge about and facilitate access to healthcare services [4,5,21,52,80]. Controversies and unresolved issues in active TB case finding among urban hard-to-reach groups have been recently addressed [10]. Contact tracing may not be feasible or effective for all urban risk groups, but can be in specific populations such as household or professional contacts [5,13]. Indiscriminate radiographic screening of immigrants is described as inefficient and not cost-effective [10,76,79,81,82]. However, some interventions that may not be effective when applied to the general population may be highly effective or cost-effective when targeted at specific urban high-risk groups, for example, homeless people and prisoners [10,16,17,19, 83–85]. Studies on longitudinal radiographic screening programmes for urban risk groups in the EU are limited but provide evidence that socially excluded and vulnerable urban risk groups can be reached [18,86], and that TB transmission can be controlled [16,19]. The National Institue for National Health and Care Excellence (NICE) has recently published guidelines advising TB screening in hostels for homeless people and prisons [11,87]. ECDC and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) have recently published guidance on prevention and control of infectious diseases in people who inject drugs [88].

### Recommendations

Big city TB control programmes should:

4.1. implement and monitor contact tracing according to national guidelines and international best practice consensus [21,78,89¬–91];

4.2. ensure that national guidelines for screening of immigrants are implemented [77];

4.3 consider targeted radiographic screening (e.g. mobile or static digital X-ray units) of urban high-risk groups, especially homeless people, people with drug and alcohol misuse, and prisoners [11,16–19,83,85];

4.4 implement measures such as TB 'one-stop shops' to ensure that suspected TB cases in urban high-risk groups are not lost before confirmation or exclusion of disease [11,21,63].

## Case holding and treatment

### General background

After case detection, TB control is founded on supporting patients to start and complete a long and occasionally complicated (e.g. due to adverse effects) course of treatment. The impact of poor compliance can be profound, both to the patient and to public health [31]. Treatment adherence is dependent on factors related both to the patient (e.g. language barriers or lifestyle factors) and to the provider (e.g. accessible, acceptable, adequate, appropriate and flexible services including treatment supervision and enhanced case management). Treatment supervision, such as directly observed therapy (DOT), requires adequate staffing levels based upon TB notification rates [4,5,80,92]. Enhanced case management requires multidisciplinary services such as specialist TB nurses, outreach social workers, TB link workers (or peer-support workers) with attention for any legal, social, housing or financial problems [5,17,46,47]. Conventional incentives and enablers, such as prepaid travel cards for public transport, can be used to increase adherence, as well as monetary incentives, which are controversial but have been demonstrated to be effective [93]. Innovative ways to increase adherence to TB treatment using modern technology should be explored as they have been in the field of human immunodeficiency virus (HIV) infections [22,23,94,95]. When patients are either too medically or socially complex to be treated in a general hospital or on an outpatient basis, modern-day sanatoria can be invaluable [96,97]. Cohort reviews are key to improving case management and have played a major role in increasing treatment completion rates [7,98,99].

### Case holding and treatment and big cities

Failure to attend appointments with medical or public health services is well-known among certain urban risk groups for TB [4,15]. For immigrants, factors such as legal, cultural, and language issues, socio-economic barriers and lack of knowledge about the healthcare system can result in taking the wrong medication or poor treatment adherence [100]. People who are homeless, or who have a history of drug or alcohol misuse, or of imprisonment, are all groups associated with poor adherence, and comprised 44% of cases lost to follow-up in London [7,31,101]. However, treatment completion can be very high among drug and alcohol misusers and homeless people in an adequate urban TB control programme with strict treatment supervision and potential mandatory isolation [16]. For case holding in big cities, the TB control programme should closely cooperate with related services, such as HIV programmes [63], services for people with a history of drug and alcohol misuse [88], prison services [102], asylum seeker services [53], and services for homeless people [13,16]. The use of supervised housing for homeless TB patients appears to be both effective and cost-effective [49, 50]. Outreach services can reduce hospitalisation and therefore costs [103, 104]. Establishment of TB link workers can reduce failed attendance through use of telephones, SMS reminders or accompanied referrals [17,22,23,46,47]. Specific attention is needed for undocumented migrants to ensure completion of treatment [52].

### Recommendations

Big city TB control programmes should:

5.1. be complemented with social support systems directed towards the different risk groups, such as accommodation for homeless people or access to methadone replacement programs for people with drug misuse [11,49,50,88];
5.2. identify patients who can benefit from DOT prior to treatment, with DOT being considered for patients with risk factors for non-adherence as part of a patient-centred care plan [11,63,105,106];
5.3. provide low-threshold and accessible services that are staffed according to TB notification rate and establish partnerships with other relevant healthcare providers working with groups at high risk of TB, to support treatment continuity [4,5,11,47,63,107,108];
5.4. consider provision of incentives and enablers, peer-support workers and modern information technology to improve treatment adherence and outcomes [11,17,22,23,46,47,93,94];
5.5. be supported by EU healthcare regulation allowing undocumented migrants to complete TB treatment in the country of diagnosis [52-54].

## Latent tuberculosis infection

### General background

The primary aim of screening for LTBI is to prevent TB disease. Aspects of active screening for LTBI in the EU [76], a European consensus statement on TB contact tracing [78], ECDC guidance on the use of interferon-gamma release assay (IGRA) for diagnosis of LTBI [109], and controversies and unresolved issues regarding LTBI screening of immigrants and urban risk groups, including cost-effectiveness [10], have been published elsewhere. Screening for LTBI should be risk-based and not population-based [110,111]. Priority for LTBI screening in EU countries is usually given to recent contacts, children, immunocompromised patients and healthcare workers [112].

### Latent tuberculosis infection and big cities

Recent immigrants, who are usually overrepresented in big cities, and urban risk groups for TB are often screened for TB disease [16,17,77,113]. Testing for LTBI is less frequently reported [6,76]. Screening of immigrants for LTBI can be cost-effective depending on preventive treatment completion [10,81,114] but is often poorly implemented [115] and the expected reduction of TB incidence has been questioned [116]. Immigrant screening can be performed in primary care settings in big cities [58, 59] and this location has been reported to be acceptable to the immigrant population [117]. The management of LTBI in urban risk groups such as homeless people or people with drug misuse is controversial. Although the prevalence of LTBI is likely to be higher than in the general population, screening opportunities are limited by the hard-to-reach and hard-to-treat characteristics of these subgroups. Additionally, drug and alcohol misuse and co-infection with HIV or other blood-borne viruses increase the probability of adverse reactions to preventive treatment [10,13]. Identification of active TB among homeless people was found to be more important [118]. The prevalence of LTBI upon detention in European prisons can be high, but diagnosis of TB disease usually remains the priority [119,120]. Novel approaches to improve preventive treatment completion in deprived populations, such as shorter or simpler regimens, are urgently needed, and should be implemented as they have been in the United States [10,121,122].

### Recommendations

Big city TB control programmes should
6.1. offer LTBI screening to urban risk groups only when an effective programme exists for active case finding and holding in these groups;
6.2. offer LTBI screening according to national guidelines, accompanied by a clear plan on preventive treatment;
6.3. organise a risk-based approach to LTBI screening, prioritising people who are at highest risk of infection or progression [63,78,112,123].

## DNA fingerprinting

### General background

Recent advances in molecular biology have provided new tools to better comprehend the epidemiology and transmission of TB disease. *Mycobacterium tuberculosis* strain genotyping or DNA fingerprinting has been widely used in population-based studies to determine the extent of ongoing TB transmission and risk factors in various communities [124,125]. Insights and applications of DNA fingerprinting in TB control have been described in review articles [126–128]. In the ECDC follow-up to the EU Action Plan to fight TB, genotyping of *M. tuberculosis* was proposed as a useful way of systematically monitoring disease transmission [129].

### DNA fingerprinting and big cities

The contribution of DNA fingerprinting to conventional epidemiological data in the context of urban TB control has been described elsewhere [125]. Briefly, molecular indications for epidemiological links and identification of risk factors for transmission are crucial for understanding the specific epidemiology of TB in big cities, allowing the detection of risk groups and informing (targeted) public health interventions [13,16]. Urban TB cases are more often seen in foreign-born patients than cases in rural areas because of the higher proportion of migrant population in these cities. Most of these cases have a reactivation of an infection acquired in the patient's native country [26] However, DNA fingerprinting has revealed that in urban migrant cases, transmission is frequently also recent, more often than in non-urban migrant cases [24]. Molecular epidemiological studies identified factors for a higher risk of clustering, reflecting the risk of infection, such as alcohol or intravenous drug misuse, homelessness, or certain ethnic backgrounds [125]. They also confirmed high-risk sites for TB transmission in big cities, including congregate settings such as shelters for

homeless people or prisons. Fingerprinting can also support extension of outbreak investigations and has been used to monitor trends and evaluate interventions, most specifically in urban areas [130].

### Recommendations

Big city TB control programmes should:

7.1. complement routine surveillance activities and contact tracing with molecular epidemiology to identify unexpected spreading of TB and outbreaks, and to evaluate interventions [125].

## General policy, legal framework and organisation of services

### General policy: general background

Organisation and policies of TB control in the EU have been discussed in review articles covering standards of care [63], contact tracing [78], immigrant screening [77], active case finding [76] and cost-effectiveness [112]. The organisation as well as the legal framework for TB control differs between EU countries. These differences reflect variations in service delivery models, infectious disease law, public health responsibilities, organisation and legal background of screening and the implementation of mandatory isolation [79].

### General policy and big cities

Organisational aspects of big city TB control have recently been described [5]. Lack of central planning, political commitment and mechanisms to commission city-wide services have created barriers to implementation of evidenced-based and cost-effective services for case finding and case holding [17]. Increasing rates of TB have been found where big city TB control systems are fragmented and involve a high number of clinical settings [4,131]. Many of the high-risk TB patients found in big cities have complex social, medical and economic needs, and multi-disciplinary teams, networking, for example, with experts in relevant co-morbidities such as HIV and hepatitis C and community and patient groups and sharing of experience between practitioners, are important in the organisation and provision of care in these settings.

### Legal framework general background

Multiple laws can provide the legal framework for TB control in a country. Infectious disease acts and reports regulate the various responsibilities of national and local authorities, notification or reporting and surveillance of TB or TB-HIV, screening and mandatory isolation in case of threats to public health [132–134]. International legislation (e.g. Universal Declaration of Human Rights European Convention on Human Rights [135,136]) state that any application of restrictions, including mandatory isolation, requires (i) a legal basis and (ii) reasonable evidence that the restrictions are necessary to protect public health. The public health argument for compulsory TB screening of immigrants and mandatory isolation is sometimes questioned [137,138].

### Legal framework and big cities

A legal framework for notification should provide the information for surveillance, cross-sectional studies and cohort reviews in big cities. [7,98,99] Non-compliant infectious TB patients are common in EU big cites, especially among urban TB risk groups [31]. The use of mandatory isolation is rarely used in some big cities in the EU [139]. Legal frameworks for mandatory isolation can be part of a successful urban TB control programme, if implemented when extensive attempts to support the patient have failed, for example through DOT, incentives and enablers, and social support [16].

### Recommendations:

Big city TB control programmes should:

8.1. be supported by high-level political commitment;

8.2. be organised to ensure accessibility for patients and include sufficient staff and expertise [4,5,11,80];

8.3. promote strong collaboration and coordination between sectors as a prerequisite to ensure delivery of the proposed recommendations;

8.4. have community and patient engagement programmes and address the problem of stigmatisation [58–61];

8.5. use involuntary isolation only as a measure of last resort under humane conditions;

8.6. contribute to a European network to facilitate the exchange of experience between programmes and allowing external assessment.

## Strategy, monitoring and evaluation

### General background

To reach and sustain the goal of eliminating TB in Europe it is fundamental that countries develop strategic TB control plans tailored to their own epidemiological situation. The ECDC *Framework Action Plan to fight tuberculosis in the European Union* and its follow-up provides areas for strategy development, including monitoring and evaluation, which can serve as a basis for a country's plan [28, 129]. Outcome assessment should be supported by robust and quality-assured surveillance and laboratory systems, and linked to molecular epidemiology where possible [28,129]. Systematic cohort reviews are of great value to improve the quality of data for every TB case and are key to the evaluation of TB control programmes by identifying problematic issues and gaps in case management [7,98].

### Strategy, monitoring and evaluation of TB programmes and big cities

In countries where there is an identified problem with TB accumulating in vulnerable groups in big cities, the TB control strategy should be adapted to target those specific challenges and needs. Evaluation of big city TB programmes, internal and external, should be performed regularly in order to identify gaps in services and be based upon ECDC-proposed indicators to monitor progress towards elimination [129], such as notification rates (including sputum smear positive

TB), paediatric TB, diagnostic delay, treatment adherence rates, treatment outcome, cost-effectiveness and social support [5,17,99]. High-risk deprived communities as well as civil society can be engaged in such a process. DNA fingerprinting can monitor trends and evaluate interventions, most specifically in urban areas [16,19,125].

## Recommendations

Big city TB control programmes should:

9.1. implement a continuous process of programme evaluation that will inform strategy development and include independent external peer review;

9.2. perform review of case detection and cohort review of case management and treatment outcome. Reviews should include analysis by urban risk group [98, 140];

9.3. collaborate to evaluate targeted interventions in big cities, such as molecular epidemiology, to establish additional benefits in TB control [125].

## Conclusion

In low-incidence EU countries TB is increasingly concentrated in big cities. There is an urgent need for the systematic implementation of effective, cost-effective, evidence-based and innovative approaches and tools to improve early case finding, case holding and treatment completion in metropolitan areas, especially among vulnerable groups [28]. The working group for TB control in big cities and urban risk groups in the EU has formulated 32 recommendations for big city TB control in nine areas of possible interventions. These recommendations resulted from a consensus process, and were prepared as precisely as possible but owing to the consensus approach, some were formulated as considerations. This was necessary because the epidemiological background of TB may differ between big EU cities, some interventions may not be available in all countries and cities, and there are limitations to what the working group can instruct EU Member States to do. Some of the recommendations are not strictly specific to big cities, because there is some overlap between urban TB control and general principles, and therefore the working group agreed not to mention certain issues, such as nosocomial IC, in the recommendations, when it was considered to be a general principle. Overall, this consensus statement demonstrates that at present the level of evidence for these recommendations to achieve control of TB in EU cities and among urban risk groups is limited and should be improved. Exchange of experience, collaborative research, advocacy and cooperation between different urban TB programmes in the EU will be instrumental to achieving TB control.

## Conflict of interest

None declared.

## Authors' contributions

The first draft of the manuscript was written by RvH, GdV, RA and IA. All authors contributed to revisions and intellectual content of the paper and have seen and agreed the final version of the manuscript.

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