High burden of extended-spectrum $\beta$-lactamase-positive *Escherichia coli* in geriatric patients

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Few studies have described how an expanding elderly population influences the burden of antimicrobial resistance in micro-organisms. This study aimed to investigate trends in age-stratified extended-spectrum $\beta$-lactamase (ESBL)-positive *Escherichia coli* metrics in relation to an ageing population. The antimicrobial resistance database of *E. coli* from a healthcare region in Hong Kong from 2003 to 2012 was retrospectively reviewed. Future trends in age-stratified ESBL metrics were predicted up to 2022. Susceptibility results of clinical *E. coli* isolates from patients aged 0–74 years (n = 17 853) and aged $\geq$ 75 years (n = 17 047) were analysed. For the period 2003–2012, 23.7% of the hospital admissions were of patients aged $\geq$ 75 years. However, approximately half of the annual ESBL-positive *E. coli* isolates were recovered from patients aged $\geq$ 75 years, being 55.0% (233/424) in 2003 and 56.0% (639/1142) in 2012. During this period of time, the annual prevalence and cumulative incidence of ESBL-positive *E. coli* in patients aged $\geq$ 75 years were significantly higher than in patients aged 0–74 years. From 2012–2022, it is predicted that ESBL-positive *E. coli* prevalence among patients aged 0–74 years and $\geq$ 75 years would increase from 25.4% to 50.2% and from 30.8% to 70.0%, respectively. In 2022, the predicted ESBL-positive *E. coli* cumulative incidence would be 63.7 per 10 000 admissions and 178.7 per 10 000 admissions among patients aged 0–74 years and $\geq$ 75 years, respectively. In conclusion, a rapidly expanding elderly population would substantially add to the burden of ESBL.

INTRODUCTION

Population ageing is under way in many developed countries. In Hong Kong, the problem is particularly severe because of a long life expectancy and low birth rate (Census and Statistics Department of Hong Kong Special Administrative Region, 2013). In the last decade, the elderly dependency ratio (defined as the number of people aged $\geq$ 65 years per 1000 people aged 15–64 years) increased from 162 in 2003 to 183 in 2012. It is projected that the ratio will reach 286 in 2022 (Census and Statistics Department of Hong Kong Special Administrative Region, 2012). Among the geriatric populations, infections such as urinary tract infections and pneumonia are common (Htwe et al., 2007). As symptoms and signs of infections in elderly patients are often non-specific and microbiological results may not be easy to interpret in this population, misdiagnosis and over-prescription of broad-spectrum antibiotics in elderly patients have been widely reported (Bellmann-Weiler & Weiss, 2009; Caterino & Stevenson, 2012). Not surprisingly, numerous surveillance studies have identified old age to be a major risk factor for antimicrobial resistance (Ho et al., 2007; Safdar & Maki, 2002; Sanchez et al., 2013). Although the association between old age and antibiotic resistance is well recognized, few studies have described how an expanding elderly population may impact upon the burden of antimicrobial resistance. In the past decade, a major issue in *Escherichia coli* infections is the rapid emergence of extended-spectrum $\beta$-lactamases (ESBLs) (Ho et al., 2007; To et al., 2013). In a recent multi-centre surveillance in Dutch hospitals, the majority of highly resistant Gram-negative rods were ESBL-producers (Willemsen et al., 2011). Therefore, we used the microbiology database for *E. coli* from a healthcare region in Hong Kong to assess how projected population ageing may affect the future burden for this type of antimicrobial resistance.

METHODS

Data sources. This was a retrospective analysis of data collected for other purposes. The computerized database in a hospital-based clinical microbiology laboratory in Hong Kong was used. This
laboratory provides a service for a network of five hospitals, including a 1400-bed acute care university teaching hospital with all the clinical disciplines, including renal, liver and bone marrow transplantation services and four convalescence care hospitals with 110–524 beds. The hospital network provides a clinical service to a population of approximately 0.53 million. Admission figures to the five hospitals were obtained from the record office. From 2003 to 2012, the data for E. coli were extracted, and duplicate isolates were removed according to the ‘first isolate per patient per calendar year’ method. Only E. coli isolates that originated from clinical samples (including blood, other body fluids, wound, urine and respiratory specimens) were included while faecal specimens, infection control specimens and non-clinical samples were excluded. Isolates that originated from outpatients were also excluded. During this period, all isolates were tested by the disc diffusion method according to the Clinical and Laboratory Standards Institute (CLSI, 2012), and ESBL production was confirmed by the double disc synergy test (Ho et al., 1998). Laboratory practice with regard to identification to species level and sensitivity testing for coliform bacteria remained unchanged over the entire period. Two metrics were used to assess quantitative changes in the annual resistance burden of ESBL-positive E. coli isolates: (1) the prevalence as defined by the proportion (%) of ESBL-positive E. coli isolates among all E. coli isolates, and (2) the cumulative incidence as defined by the annual number of ESBL-positive isolates per 10 000 patient admissions.

**Regression analysis.** Historical time trends in admission figures and ESBL-positive E. coli metrics were assessed by simple linear regression, with time as the covariate. Separate models were fitted for patients aged below 75 and those aged 75 and above. Prediction of ESBL-positive cumulative incidences was based on historical time trends. It was assumed that the linear temporal trend in the age-specific cumulative incidence continued to 2022. The age-specific cumulative incidence was predicted by extrapolating the linear regression model with age group, time and interaction between age and time as covariates. It was assumed that the linear relationship between population size and number of admissions continued to 2022. The age-specific number of admissions was predicted by extrapolating the linear regression model with age group and population statistics as covariates. Prediction of admission numbers was based on linear regression models with age group and age-specific population data in Hong Kong provided by the Census and Statistics Department (2003–2012: observed population; 2013–2022: projected population) (Census and Statistics Department of Hong Kong Special Administrative Region, 2012). Finally, age-specific crude incidence of ESBL-positive E. coli was predicted by multiplying the predicted age-specific cumulative incidence and the predicted number of admissions, then dividing by 10 000. Age-specific crude incidence of ESBL-negative E. coli was predicted in the same manner. The prevalence of ESBL-positive E. coli was obtained by dividing the predicted ESBL-positive crude incidence by the sum of the predicted ESBL-positive and ESBL-negative crude incidences.

Monte Carlo simulation was used to construct 95 % confidence intervals for the estimates. A P value of 0.05 was considered to indicate statistical significance. The data were analysed by SPSS Statistics version 20.0.

**RESULTS**

**Historical time trends in admission figures and ESBL-positive E. coli metrics**

During the study period, there were a total of 34 900 E. coli isolates from hospitalized patients including 7966 ESBL-positive E. coli isolates and 26 934 ESBL-negative E. coli isolates, hence an overall ESBL prevalence of 22.8 %. The prevalence of ESBL in the different age groups was: 0–50 years, 15.9 % (1376/8653); 51–64 years, 25.4 % (1089/4281); 65–74 years, 24.5 % (1206/4919); ≥ 75 years, 25.2 % (4295/17 047). The prevalence of ESBL in the different specimen sources was similar: blood, 22.2 % (717/3234); urine, 23.7 % (5335/22 495); other body fluids, 22.9 % (362/1578); wound, 19.7 % (1021/5182); respiratory, 22.0 % (531/2411). The total denominators for the cumulative incidence calculations included 1 523 297 admissions of which 360 507 (23.7 %) admissions were of patients aged ≥ 75 years. The temporal changes in the number of admissions and the ESBL-positive E. coli metrics from 2003 to 2012 were analysed (Table 1). The annual number of ESBL-positive E. coli isolates had increased 2.7-fold from 424 in 2003 to 1142 in 2012. Statistically significant increases were observed for the two ESBL-positive E. coli metrics in those aged 0–74 years and those aged ≥ 75 years. Over this period, 20.1 % (in 2003) to 25.9 % (in 2012) of the annual admissions were of patients aged ≥ 75 years. However, approximately half of the annual ESBL-positive E. coli isolates were recovered from patients aged ≥ 75 years, being 55.0 % (233/424) in 2003 and 56.0 % (639/1142) in 2012. In all years, the annual prevalence and cumulative incidence of ESBL-positive E. coli in patients aged ≥ 75 years were significantly higher than those in patients aged 0–74 years (P<0.001).

**Predicted ESBL-positive E. coli metrics**

Observed and predicted parameter estimates for prevalence and cumulative incidence of ESBL-positive E. coli are presented in Table 2 and Fig. 1. The results showed that both ESBL metrics are predicted to increase faster in patients aged ≥ 75 years than in patients aged 0–74 years between 2012 and 2022. In both age groups, greater increases in the prevalence and cumulative incidence of ESBL-positive E. coli were predicted in 2012–2022 compared with 2003–2012. The total change anticipated in ESBL-positive E. coli prevalence in 2012–2022 from this model was +24.8 % and +39.2 % among patients aged 0–74 years and aged ≥ 75 years, respectively (Table 2). The total change in ESBL-positive E. coli cumulative incidence was +26.3 per 10 000 admissions and +43.0 per 10 000 admissions among patients aged 0–74 years and aged ≥ 75 years, respectively.

**DISCUSSION**

This study shows a high burden of ESBL-positive E. coli in our healthcare region where approximately half of all ESBL-positive isolates originated from patients aged ≥ 75 years. Linear regressions were used to construct future estimates by using previously observed data. Monte Carlo simulations were then used to assess the uncertainty in the future estimates and the simulations were expressed graphically (Fig. 1). The study is unique in using two
resistance metrics to describe the change in the burden of ESBL in the last decade and its future evolution in relation to the predicted ageing population. The large burden of ESBL seen in the study is in agreement with recent studies, which highlighted the wide dissemination of this resistance mechanism in many countries (Ho et al., 2007, 2008, 2011a, 2012b). In the USA, a recent nationwide survey showed that annual hospitalization due to ESBL-positive E. coli had increased threefold from 5.1 per 10 000 admissions in 2000 to 18.1 per 10 000 admissions in 2009 (Zilberberg & Shorr, 2013). Worldwide, the rapid rise in the incidence of ESBL was predominantly attributed to the successful dissemination of CTX-M enzymes among E. coli isolates causing urinary and bacteraemic infections (Ho et al., 2011b, 2012b; Naseer & Sundsfjord, 2011). In Hong Kong, previous studies have found that CTX-M enzymes were present in >90% of the community and hospital ESBL-positive E. coli isolates (Ho et al., 2007, 2008, 2012a).

Table 1. Historical data used in the estimation of the future burden for ESBL-positive E. coli

<table>
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<th>Annual figures</th>
<th>R²</th>
<th>P</th>
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<tbody>
<tr>
<td>Aged 0–74 years*</td>
<td></td>
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<tr>
<td>Patient admissions</td>
<td>105.4</td>
<td>109.2</td>
<td>110.6</td>
</tr>
<tr>
<td>Number of isolates</td>
<td>191</td>
<td>257</td>
<td>301</td>
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<tr>
<td>Prevalence</td>
<td>11.7</td>
<td>14.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>18.1</td>
<td>23.5</td>
<td>27.2</td>
</tr>
<tr>
<td>Aged ≥75 years</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patient admissions</td>
<td>26.5</td>
<td>29.0</td>
<td>30.1</td>
</tr>
<tr>
<td>Number of isolates</td>
<td>233</td>
<td>308</td>
<td>307</td>
</tr>
<tr>
<td>Prevalence</td>
<td>16.3</td>
<td>20.3</td>
<td>19.5</td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>88.0</td>
<td>106.3</td>
<td>101.9</td>
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*Patient admissions figures are given in thousands. Two metrics were used to evaluate temporal changes in the burden of ESBL type of antimicrobial resistance in E. coli: prevalence, proportion (%) of ESBL-positive E. coli among all E. coli isolates; cumulative incidence, number of ESBL-positive E. coli isolates per 10 000 patient admissions.

Table 2. Predicted age distribution of the population, patient admissions and ESBL-positive E. coli metrics in 2022 and comparison with figures in 2003 and 2012

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<tbody>
<tr>
<td>Aged 0–74 years</td>
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<tr>
<td>Population (thousands)</td>
<td>6404.7</td>
<td>6659.9</td>
<td>7106.4</td>
<td>+ 255.2</td>
<td>+ 446.5</td>
</tr>
<tr>
<td>Patient admissions (thousands)</td>
<td>105.4</td>
<td>134.6</td>
<td>185.3 (175.2–195.1)</td>
<td>+ 29.2</td>
<td>+ 50.7</td>
</tr>
<tr>
<td>Crude incidence (no.)</td>
<td>191</td>
<td>503</td>
<td>1180.8 (795.5–1616.5)</td>
<td>+ 312.0</td>
<td>+ 677.8</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>11.7</td>
<td>25.4</td>
<td>50.2 (31.6–100)</td>
<td>+ 13.7</td>
<td>+ 24.8</td>
</tr>
<tr>
<td>Cumulative incidence, per 10 000 admissions</td>
<td>18.1</td>
<td>37.4</td>
<td>63.7 (43.1–86.9)</td>
<td>+ 19.3</td>
<td>+ 26.3</td>
</tr>
<tr>
<td>Aged ≥75 years</td>
<td></td>
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<td></td>
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<tr>
<td>Populations (thousands)</td>
<td>326.1</td>
<td>494.7</td>
<td>614.0</td>
<td>+ 168.6</td>
<td>+ 119.3</td>
</tr>
<tr>
<td>Patient admissions (thousands)</td>
<td>26.5</td>
<td>47.1</td>
<td>59.9 (54.5–64.8)</td>
<td>+ 20.6</td>
<td>+ 12.8</td>
</tr>
<tr>
<td>Crude incidence (no.)</td>
<td>233</td>
<td>639</td>
<td>1070.5 (901.4–1235.9)</td>
<td>+ 406.0</td>
<td>+ 431.5</td>
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<tr>
<td>Prevalence (%)</td>
<td>16.3</td>
<td>30.8</td>
<td>70.0 (55.9–92.9)</td>
<td>+ 14.5</td>
<td>+ 39.2</td>
</tr>
<tr>
<td>Cumulative incidence, per 10 000 admissions</td>
<td>88.0</td>
<td>135.7</td>
<td>178.7 (156.1–202.1)</td>
<td>+ 47.7</td>
<td>+ 43.0</td>
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*Figures in parentheses represent confidence intervals based on simulations.
Our data corroborate previous work in that advanced age is indeed a risk factor for ESBL, indicating that extended-spectrum cephalosporins may no longer be the appropriate empirical therapy for the treatment of urinary, intra-abdominal and bacteraemic infections in geriatric patients (Hsueh et al., 2011; Solomkin et al., 2010; To et al., 2013). The cautionary use of cephalosporins as empirical therapy for suspected or confirmed *E. coli* infections should be extended to other countries where the ESBL burden is also high (Sartelli et al., 2013; Solomkin et al., 2010; To et al., 2013).

This study provides an estimation of the burden of ESBL in the coming decade if this resistance mechanism continues to increase at the current speed. The massive increase in the burden of ESBL-positive *E. coli* shown in our study is multifactorial. Firstly, Hong Kong is one of the world’s most densely populated cities. Through analysis of the biological, temporal and spatial data, Jones et al. (2008) showed that human population density was a common significant independent predictor of emerging infectious disease events including newly evolved strains of drug-resistant bacteria. Secondly, huge reservoirs of ESBL genes

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**Fig. 1.** Predicted temporal trends for two ESBL-positive *E. coli* metrics in patients aged 0–74 years and patients aged ≥75 years. (a) Prevalence. (b) Cumulative incidence.
exist in our community and within the population of food animals produced for human consumption. In an investigation of faecal carriage of ESBL-producing organisms in 2007–2008, the prevalence of CTX-M-producing bacteria was 20.7% in household children and 50.3% in household adults (Lo et al., 2010). Molecular typing of the CTX-M-producing isolates demonstrated that the strains from the same households were mostly unrelated and only a small proportion of them were clonally related (Lo et al., 2010). Hence, acquisition from contaminated food and water could be playing a more important role than transmission within a household (Depoorter et al., 2012; Lo et al., 2010; Manges & Johnson, 2012). Among food animals produced for consumption in Hong Kong, 8/10 chickens and 7/10 pigs were found to carry ESBL-positive E. coli isolates (Ho et al., 2011a). Finally, the rise in ESBL-positive E. coli is partly a consequence of the higher incidence of E. coli in the elderly (Kennedy et al., 2008), thereby increasing the population at risk. We estimated that approximately 25–39% of the increase in the ESBL-positive E. coli isolates that we observed over the past decade could be attributed to the increase in the elderly patient population aged ≥75 years (data not shown).

The control of ESBL-positive bacteria has become a major challenge. There is little doubt that humans could acquire antibiotic-resistant E. coli and its resistant genes through the food chain (Ho et al., 2011a, 2012a). Appropriate strategies are required to reduce the danger of resistant bacteria in foods (Aidara-Kane, 2012; Collignon, 2013). The incidence of resistance in bacteria in food animals has decreased after antibiotic use was banned or reduced (Dutil et al., 2010). The successful strategy in controlling foodborne resistant bacteria in Denmark should be discussed and pilot tested as a matter of urgency in other countries (Collignon, 2013). In ESBL infections, delay in the institution of appropriate therapy is common and has been associated with increased mortality and longer length of hospitalization (Stewardson et al., 2013; To et al., 2013). Hence, this growing prevalence of ESBL calls for a wider use of methods for the rapid detection of ESBL (Nordmann et al., 2012; Tamma et al., 2013). This is because fear of ESBL infection drives the use of empirical carbapenems, and such shifts in antibiotic strategy may add to the selection for carbapenemase producers (Tzouvelekis et al., 2012).

The strength of this study was that ESBL data spanning a decade were used to assess the historical trends and to make predictions. Furthermore, we made use of the official population projections from the Census and Statistics Department to predict the number of admissions, thus increasing the validity of the prediction. However, this study was subject to certain limitations. Firstly, data from only five hospitals were available. We implicitly assumed all the 41 hospitals in Hong Kong followed the same trends. Secondly, we assumed a linear trend in the cumulative incidence, and the linear relation between population size and number of admissions continuing in the next decade. The precision of the extrapolated number of admissions and the cumulative incidence decreased with time, as shown graphically by the confidence intervals constructed from Monte Carlo simulations being wider towards 2022. Nevertheless, the precision was taken into account by presentation of the confidence intervals. Finally, the shape of any epidemic curve cannot be predicted with absolute certainty and ESBL prevalence may level off as potentially suggested by the data in 2010–2012. Hence, the predicted figures should be interpreted with some caution.

In summary, ESBL is a major public health threat where a rapidly expanding elderly population would add substantially to the burden of this antibiotic resistance mechanism. It is important that more attention is directed to the risk management options of antimicrobial resistance in the geriatric population.

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