Are healthcare economics a factor behind European MRSA rates?

M. A. Borg

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Title: Are healthcare economics a factor behind European MRSA rates?

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Keywords: MRSA, infant mortality rate, gross domestic product, Europe, EARSS.

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Abstract: This study assessed the relationship between MRSA prevalence in 26 European countries with two key socioeconomic parameters, namely gross domestic product per capita (GDP) as well as infant mortality rate (IMR). Whilst no significant relationship was identified between MRSA and GDP (Spearman correlation: -0.387; 95%CI: -0.674 to 0.000; $p = 0.0528$), a significant correlation was evident between MRSA and IMR (Spearman correlation: 0.545; 95% CI: 0.208 to 0.766; $p = 0.005$). Elimination of a widely outlying data point retained significance. Various studies have shown IMR to be a good marker of healthcare expenditure and it is therefore reasonable to postulate that one possible factor in the multifactorial epidemiology of MRSA in Europe is the level and effectiveness of healthcare expenditure within the individual countries.

Thank you for your letter and request for revision of my manuscript. I have performed a thorough revision based on the referee's comments as well as the specific requests as per below:

Two version are being forwarded; one with track changes to allow you to identify the changes made in line with the referee's requests and one in which the track changes have been removed.

I hope that the new amended version will be found suitable for publication.

Yours sincerely

Michael A. Borg

Reviewer #1:

1. EARSS data do not represent MRSA prevalence but only MRSA proportion of Staphylococcus aureus bloodstream isolates, as author correctly has said in the lines 34-36. This should be consistently used throughout the article.

I would respectfully disagree with the referee on this point. The EARSS group has published evidence of a clear correlation between proportion and incidence (de Kraker et al 2006). By extrapolation, I believe that the inferences to MRSA prevalence & incidence within the manuscript are therefore justified. The reference has been added to the manuscript to clarify similar doubts in the readers.

2. The addition to the abstract of Spearman correlation data after eliminating widely outlying data point would give the reader better insight into the problem even after reading the abstract.

This has been added to the abstract.

Reviewer #3:

One major concern I have with his Methods is the use of multiple linear regression with MRSA proportions as the dependent variable. Observing the X axis of Figure 1, it is clear that MRSA prevalence is not normally distributed and that it is skewed to the right. Using a non-normally distributed dependent variable in linear regression may lead to false conclusions. The author will need to either transform MRSA proportion into a normally distributed variable, or rely on Spearman's rho alone as his main analyses.

All references to the linear regression calculation have been removed.

The author also notes some valid limitations to his study. One major limitation he does not address is the generalizability of his analyses outside of Europe. For example, the United States has high per capita healthcare expenditures, but a high infant mortality rate relative to per capita GDP and high MRSA prevalence. The author should note this is an additional limitation to his analyses.

I thank the referee for pointing out this valid comment; as a result, the title has been amended to specify the European focus of the paper. A comment has also been added in the discussion.

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Title page:

Are healthcare economics a factor behind European MRSA rates?

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* corresponding author

Conflict of interest: The author does not have any conflict of interest to declare

Running title: **MRSA and healthcare economics**

Keywords: MRSA, infant mortality rate, gross domestic product, Europe, EARSS.

Summary:

This study assessed the relationship between MRSA prevalence in 26 European countries with two key socioeconomic parameters, namely gross domestic product per capita (GDP) as well as infant mortality rate (IMR). Whilst no significant relationship was identified between MRSA and GDP (Spearman correlation: -0.387; 95%CI: -0.674 to 0.000; $p = 0.0528$), a significant correlation was evident between MRSA and IMR (Spearman correlation: 0.545; 95% CI: 0.208 to 0.766; $p = 0.005$). Elimination of a widely outlying data point retained significance. Various studies have shown IMR to be a good marker of healthcare expenditure and it is therefore reasonable to postulate that one possible factor in the multifactorial epidemiology of MRSA in Europe is the level and effectiveness of healthcare expenditure within the individual countries.

Over recent years, public awareness and interest in meticillin resistant *Staphylococcus aureus* (MRSA) has increased significantly. One reason for this has been the greater availability of surveillance data at pan-European level through good quality comparable data from the successful European Antimicrobial Resistance Surveillance System (EARSS) [www.rivm.nl/earss] [1]. This preliminary study attempted to determine relationships between MRSA prevalence at country level and two key socioeconomic parameters: gross domestic product per capita (GDP) as well as infant mortality rate (IMR). The GDP of a country is defined as the market value of all final goods and services produced within that nation in a given period of time. It is used by economists as a way of measuring the size of a country's economic strength and purchasing power. IMR refers to the number of newborns dying within their first twelve months of age, divided by the number of live births during that year. IMR has been used as a useful indicator of a country's level of health development; in fact, public spending on health and better access to healthcare facilities are critical determinants of IMR [2,3].

Data was obtained from publically available documents. MRSA figures for the year 2005 were sourced from the EARSS annual report 2005 (National Institute for Public Health and the Environment, Bilthoven, The Netherlands). This reported, amongst others, the proportion of *Staphylococcus aureus*, isolated from routine blood cultures, that were identified as meticillin resistant by the participating laboratories within the EARSS project during the year 2005. In turn, MRSA proportions have been shown to be strongly correlated to incidence [4]. GDP and IMR statistics for the same year were obtained from the CIA world handbook 2005 (Central Intelligence Agency Washington, USA). Respective data per country were then inputted in Excel (Microsoft Excel 2003, Microsoft Corp) for preliminary evaluation. Spearman correlation was used to compare the results of countries, arranged hierarchically according to their MRSA proportions, versus their respective GDP and IMR statistics. Analyses were performed in Medcalc, version 9.2.1.0 (Medcalc Software, Mariakerke, Belgium). A p value of 0.05 was taken to indicate statistical significance.

MRSA proportions from the 27 countries varied from 0.01 to 71.7% (mean: 23.41%) whilst GDP for the same countries ranged from \$8200 to \$55600 (mean: \$26351). Although the more affluent nations in Europe appeared to be the ones with better MRSA control, a substantial degree of

heterogeneity was evident. Several countries with relatively high GDP still had MRSA proportions that were much higher than those for less affluent nations. Rank correlation between MRSA proportions for the different European countries and the GDP per capita for that same country yielded a Spearman correlation index (ρ) of -0.387 (95%CI: -0.674 to 0.000) and a p-value of 0.0528.

On the other hand, when the same MRSA proportions were plotted against IMR, goodness of fit was much more in evidence with a substantial proportion of the points falling close to the line of best fit (Figure 1). This was confirmed by a Spearman correlation index (ρ) of 0.545 (95% Confidence Interval for ρ = 0.208 to 0.766) and $p=0.005$. In order to ensure that the widely outlying data point was not unduly influencing the correlation, the analysis was repeated by eliminating this data set from the analysis. Nevertheless, a statistically significant result was still obtained, albeit slightly inferior to that of the complete range; the Spearman's coefficient of rank correlation (ρ) = 0.491 (95% Confidence Interval for ρ = 0.127 to 0.738) and a p-value of 0.014.

The lack of significant relationship between the levels of GDP and MRSA proportions in the individual countries suggests that economic strength and purchasing power does not automatically result in improved prevention of healthcare associated infections such as MRSA. This is not surprising since the mere economic affluence of a nation would not necessarily translate into better healthcare outcomes unless that same economic effluence is channelled appropriately into effective expenditure and use. It is in this context that the strong relationship between IMR rates and MRSA proportions in European countries is very interesting. Indeed, Elola *et al* found that infant mortality was a better predictor of health care expenditure than was GDP [5]. Various elements of health care expenditure and quality have been linked to IMR by other authors. Babazono and Hillman suggested that perinatal and infant mortality was related to the number of hospital beds [2], whilst the number of physicians per capita was found to be a significant variable for infant mortality in 12 countries within the Organisation for Economic Co-operation and Development (OECD) [6]. Furthermore, Wolf and Gabay showed that increased medical expenditure led to improvements in several health outcomes, including infant mortality rate [7]. This would be more relevant in a region or continent, such as Europe, where public health has made substantial progress over the past

century. To a reasonable degree, these countries exhibit are no cataclysmic shifts in general living conditions between each other, as evident from the GDP per capita of all the studied countries, which was within 2 standard deviations of the median. In such a background, a major input to reducing infant mortality would therefore be the ability to increase survival in low birthweight infants where improved neonatal and obstetric services are important contributors [8].

Just as it seems to be a determinant for IMR, the degree of investment in healthcare systems would almost certainly play a critical role in determining the success or otherwise of MRSA control in the different European countries. Whilst direct references to the role of health care expenditure for improved MRSA control at a pan-national level have not been highlighted in medical literature, both capital and manpower investment within hospitals are critical to obtain effective MRSA control [9].

Despite the rationality of this argumentation, it would be unacceptably simplistic to assume that the only determinant for successful MRSA control is just the level and effectiveness of funds pumped into the country's healthcare system. This is evident from the correlation coefficient of 0.545. In addition, both sets of statistics are recognised to possess inherent sources of error. There is considerable debate on the different practices and cut-offs to define infant mortality in different countries, which of course have implications on the rate itself [10]. The MRSA proportions reported by EARSS are based on diverse population coverage in each of the participating European country. Potential bias may be present if the proportion of the population under study is either low or partial. Furthermore the model may not be applicable in other continents outside of Europe, especially if the GDP varies substantially from the European median.

Nevertheless, despite these limitations, the identified correlation between MRSA and IMR cannot be easily ignored and would justify a more extensive study into health care expenditure and utilisation and its impact on MRSA and other healthcare associated infections.

References:

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Figure 1: Scatterplot of Infant Mortality rate (IMR) per thousand live births vs %MRSA proportion (MRSA) for countries participating in the EARSS network in 2005 with line of best fit (solid line) and 95% confidence intervals (dotted lines)

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Title page:

Are healthcare economics a factor behind national-European MRSA rates?

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generated a final model in which only IMR was independently and positively associated with MRSA
proportions (regression coefficient = 2.38; $p=0.005$).~~

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36 ~~sufficient beds to avoid overcrowding [8], as well as the provision of the sufficient resources, such~~
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38 ~~as alcohol rub, to maximize hand hygiene and therefore improve MRSA control [9].~~

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Nevertheless, despite these limitations, the identified correlation between MRSA and IMR cannot be easily ignored and would justify a more extensive study into health care expenditure and utilisation ~~so as to develop possible causal models which estimate more effectively~~ and its the impact of ~~distribution of income and services~~ on MRSA and other healthcare associated infections.

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References:

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Figure 1: Scatterplot of Infant Mortality rate (IMR) per thousand live births vs %MRSA proportion (MRSA) for countries participating in the EARSS network in 2005 with line of best fit (solid line) and 95% confidence intervals (dotted lines)