HUMAN HEALTH IMPLICATIONS OF MRSA CC398 IN DENMARK

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Introduction

Methicillin-resistant Staphylococcus Aureus CC-398 (MRSA CC398) was first isolated from humans in Denmark in 2003 and from pigs in 2006 (anonymous, 2007-2015). Since then it has spread in the pig population, and a screening from 2016 found MRSA CC398 in 88 % of the screened slaughter pig herds, indicating that the majority of Danish pig herds are positive.

However, the human health consequences are less obvious, since the epidemiology and implications of antimicrobial resistance in staphylococci causing human infections is not straightforward.

Based on surveillance data from Denmark and the Netherlands, published studies from other European countries and a model developed by the European Centre for Disease control (anonymous, 2009), the human health consequences for the Danish population is evaluated.

Method

Based on data extracted form databases from the Danish national health institute (Statens Serum Institut) (anonymous, 2017) and from the DANMAP-reports (anonymous, 2007-2015), number of MRSA CC398-carriers, MRSA-infections and MRSA-bacteremias are calculated year by year, and compared to the herd prevalence (anonymous, 2007-2015, anonymous 2016).

Number of bacteremia-cases is used as input to the model developed by ECDC (anonymous 2009), calculating the extra number of deaths and extra hospital days attributed to MRSA CC 398-bacteremia.

Number of carriers in the Danish human population was estimated using data from an unpublished Danish study on carriage of MRSA CC398 in people working with pigs and household members, combined with data from Statistics Denmark (anonymous, 2017b).

Results

Based on the above mentioned sources, Alban et al, 2017, estimated the number of human carriers of MRSA CC398 to be 10,600 in 2014, based on 69% positive herds. If all herds were positive, they estimated the number of carriers to be 15,100. In the general population without contact to pigs, they estimated that 5,600 humans were carriers of MRSA CC398, or 0.1% of the general population (population of Denmark 5.5 million), if all pig herds were positive.
Figure 1 shows the number of humans with a clinical infection of MRSA CC398 without pig contact and the herd prevalence (anonymous, 2007-2015, anonymous, 2016).

The incidence of clinical cases in the human population without pig contact is directly proportional to the herd prevalence. In 2011 there were 1.1 clinical cases for each percent infected herds, in 2014 it was 1.06 and in 2016 it was 1.1. Assuming a 100% infected herds, by extrapolation it is estimated, that total number of clinical cases will be 110. Or an annual incidence of 2 out of 100,000 Danes without pig contact. Number of incident cases of clinical infection with MRSA CC398 amongst persons with pig contact was 120 in 2016.

![Graph showing the relationship between herd prevalence and human clinical incidence of MRSA CC398](image)

**Figure 1.** Incident cases of clinical infections of MRSA CC398 in Danish patients without pig contact and the MRSA CC398 herd-prevalence.

The majority of these infections are soft tissue infections, wound infections and eczemas. Bacteremias are considered the most severe Staphylococcal infection. Statens Serum Institute (anonymous, 2017) publishes each year the number of bacteremia’s caused by MSSA, MRSA and MRSA CC398. Figure 2 shows the annual number of bacteremias caused by MSSA, MRSA other than CC398 and MRSA CC398 in Denmark. MRSA CC398 constituted between 0.15% and 0.3% of bacteremias caused by Staphylococcus aureus from 2014 to 2016 (7 in 2014, 3 in 2015 and 7 in 2016), and between 10 and 18% of MRSA bacteremias. An annual incidence between 0.05 and 0.1 out of 100,000 Danes.

30 day mortality for 2014 to 2016, estimated as number of deaths within 30 days after a positive blood culture was 23% for MSSA, 20% for MRSA and 24% for MRSA CC 398. In total 4 patients died within 30 days after a positive blood culture for MRSA CC398 in the 3 years from 2014 to 2016 (anonymous 2007-2015, anonymous 2017). All patients had severe underlying disease and had the typical age profile for patients dying after Staphylococcus aureus-bacteremia (median age for patients dying within 30 days after S. aureus bacteremia is close to 80 years in Denmark (anonymous 2015)).

The model developed by ECDC (anonymous, 2009) estimates that 9.8% of bacteremias caused by MRSA will have a fatal outcome because of antimicrobial resistance, based on Cosgrove, 2003. Given an average number of MRSA CC398 bacteremias over the last three years of (7+3+7)/3=5.6, the extra annual deaths attributed to the antimicrobial resistance is 9.8% times 5.6, or 0.6 per year. Based on
the Danish estimates for mortality after MRSA-bacteremias, there are no extra deaths, because there is no additional mortality associated with bacteremias caused by MRSA in Denmark, compared to MSSA-bacteremia.

ECDC estimates that there is an increased length of hospital-stay of 8 days for patients with MRSA-infections. With 5.6 cases of MRSA CC398-bacteremias each year, there will be an extra 45 bed-days in Danish hospitals due to bacteremia caused by MRSA CC398.

Figure 2. Annual cases of bacteremias caused by Staphylococcus aureus, MRSA and MRSA CC398.

Discussion and conclusion

Estimating the human health consequences of antimicrobial resistance in zoonotic pathogens is not straight forward. Estimates are highly influenced by the assumptions. ECDC estimates the excess mortality and morbidity that is related to antimicrobial resistance, assuming that the patients would have been infected by staphylococci irrespective of resistance. This assumption is critical for the evaluation of the human health consequences. Several studies have found that staphylococci are transmitted from pigs to humans, irrespective of resistance (Armand-Lefevre, 2005, Oppliger, 2012). Sun (2015) found that US swine veterinarians carried pig related staphylococci to the same extent as Dutch swine veterinarians (Verkade, 2013). In the USA the majority of pig related staphylococci were MSSA, and in the Netherlands it was MRSA, reflecting differences in MRSA prevalence in pig herds in the two countries.

So it is probable, that if pigs contribute to the total load of staphylococci in humans, then it is not dependent on antimicrobial resistance, making it justifiable to estimate the health consequences using the ECDC-model.

Human health consequences should not only be evaluated at the present time, but also future consequences should be taken into consideration. The human population can be divided into three groups: People working with or handling live pigs (group 1), house hold members living with people working with or handling live pigs (group 2) and the rest of society (group 3).

After the MRSA CC398 is spread to all herds, group 1 and 2 will stabilize. Further increases in the human population will be because of further spread in group 3. Figure 1 indicates no increased spread in group 3, except for the spread explained by the increase in herd prevalence.
Data from Germany (van Alen, 2016) found that MRSA CC398 increased in human patients from 2005 to 2011, and then remained stable. In the Netherlands the level of MRSA CC398 in the human population has remained stable since 2010 (anonymous, 2016b).

In conclusion epidemiological evidence suggests limited spread in group 3, and no indication of increased spread in group 3 after MRSA CC398 has spread to most of the animal population at risk.

References


