WHY IS ANTIMICROBIAL RESISTANCE IN PIGS NOT SO IMPORTANT FOR PUBLIC HEALTH?

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SUMMARY

In recent years, there has been growing concern over the potential spread of antimicrobial resistance from the use of antibiotics in animals to humans, and that they may play a significant role in causing resistance in man. Lay press have expressed that up to 70% of resistance seen in man may come from the agricultural use of antibiotics – even risk assessment reports to governments say there is no hard evidence but an approximate estimate of 33-50% of resistance may come from the agricultural sector. It was the purpose of this paper to evaluate the potential risk of the transmission of infections from pigs to man either directly or via pig meat using an epidemiological basis. This could then be compared with the incidence of diseases in man caused mainly by bacteria and are likely to be treated with antibiotics. Data evaluation showed that pigs could be accountable for infections in man, especially personnel working directly with pigs. Regarding the general public, the figure was much lower at 0.0031% on a population basis, which is equivalent to 3.1 people in every 100,000. Human infections occur and are treated with antibiotics in approximately 16.34% of cases on a population basis, or 16,340 people/100,000. Therefore, pigs cause 0.019% of human cases and if all infections were resistant to antimicrobials this would be the contribution of resistance transmission. If the concern was just for 'critical use' antibiotics the figure would be as low as 0.00034% if a figure of 2% resistance is used. In conclusion, this is the reason why antimicrobial resistance transfer to the general human population from pigs can be considered of minor importance in comparison with the direct use of antimicrobials in man by doctors and in hospitals.

INTRODUCTION

Antibiotics have been extensively used in swine production over many years. There have been recent reports of outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA) CC398 in pigs starting in the Netherlands (Voss *et al.*, 2005) and now recognised across most of the European Union (EFSA, 2009, 2010). There have also been increasing reports of the presence of extended-spectrum beta-lactamase (ESBL) producing bacteria, especially *Escherichia coli* and *Salmonella* spp (EFSA, 2011a), associated with the increasing use of 3rd and 4th generation cephalosporins. Fluoroquinolone resistance has also been reported to be on the increase, especially in poultry (MARAN, 2011). As a result some countries, such as the Netherlands, have decided to reduce their antibiotic consumption in veterinary medicine by 50% by 2013. The European Commission (2011) and the European Council (2012) have outlined the review of antimicrobials in the European Union (EU) over the next five years and the details are awaited with keen interest.

However, many of the views regarding antimicrobial resistance transfer from animals to man is really speculative and it is difficult to obtain finite information of the actual risks. However, it does not stop the lay press expressing opinions of the quantity and a figure of up to **70%** has been promulgated. The Bureau of Risk Assessment and Research Programming (BuRo, 2010) reported to the Dutch Government that, *"There are no hard evidence on the actual importance of transfer of resistance from the animal to the human sector but a rough estimate is that 33-50% of the resistance observed in infectious agents for humans, comes from the agricultural sector."*

It is hard for a single person to answer these questions, where governments and European bodies seem unable to do so. However, the purpose of this paper is to try to show that the use of antimicrobials in swine and the transfer of antimicrobial resistance from pigs to man is really of low importance. An epidemiological approach will be used to try and demonstrate and quantify what the author thinks is a relatively low significance of resistance transfer from swine to humans.

The epidemiological approach – the chain of infection

It is necessary to identify the infectious agent to be evaluated; the source is the pig, the route of transmission to the host, man, the susceptibility of the host to the colonisation and infection regarding a zoonotic bacterium. If a commensal bacterium, then the rate of colonisation and resistance

Table 1 – *The chain of infection and resistance for zoonotic and commensal bacteria (Prescott et al., 2005)*

The chain	Zoonotic infection	Commensal infection
Organism	Bacteria	Bacteria
Source	Pig	Pig
Host	Man	Man
Route	Direct, indirect, food etc	Direct, indirect, food etc
Susceptibility of host	Natural defences, age, immune status	Natural defences, age, immune status
Colonisation	Yes	Yes
Infection	Yes	No (Yes – nosocomial?)
Disease incidence (%)	Yes	No (Yes – nosocomial?)
Resistance transfer	Yes	Yes
Mortality incidence	Yes	No (Yes – nosocomial?)
Treatment failure incidence	Yes	Yes

transmission from the swine bacterium to the host bacterial flora needs to be determined. A further step for commensal bacteria would be to evaluate the significance of those bacteria in the host causing infection (often nosocomial/ hospital infections) and their resistance affecting drug treatment responses.

Human bacterial infections

A list of human bacterial infections are summarised overleaf (see Table 2) and potential associations with swine identified (Prescott *et al.,* 2005; Mossad, 2010; Foxman, 2002).

Of the 49 infectious agents reported, only nine are potentially pig associated **(approximately 18%)** but they may also involve other animal species. A further bacterium, *Streptococcus suis* (*s. suis*), is also potentially transmissible to man from pigs, but usually affects farm workers or persons involved in the meat trade.

Major infections that are potentially associated with pigs

An overview of the percentage incidence of infection and mortality of some human and potentially pig associated diseases is summarised in Table 3.

If the major bacterial infections that are potentially associated with pig transmission are examined further then their impact regarding infection, disease, mortality and resistance transfer can be further assessed (see Table 4).

Streptococcus suis, Bacillus anthracis, Clostridium perfringens

Streptococcus suis has caused disease in man (Barlow *et al.,* 2003) and in the United Kingdon (UK) **21%** of stockmen were found to be seropositive. There were approximately **two cases/year** over a 20 year recording period with cerebrospinal fluid or blood isolates, with **12.5%** of cases dying from their infection. The majority of cases showed signs of meningitis and septicaemia and involved mainly pig farmers/stockmen, abattoir workers and butchers (93% of cases with epidemiological data). Resistance was not an issue as most S. suis isolates were considered penicillin susceptible in the UK.

Bacillus anthracis is uncommonly found in pigs in the UK and could possibly infect humans, closely involved with an outbreak, but the majority of isolates are considered penicillin sensitive. *Clostridium perfringens* could also potentially infect man but there is little evidence of disease. Resistance is not an issue as the majority of pig isolates are susceptible to penicillin.

Methicillin resistant Staphylococcus aureus (MRSA)

In contrast to *S. suis*, MRSA strains have been a major problem in humans, associated either with hospital infections but also increasingly in the community. The MRSA clone CC398 has been found in many EU countries in pigs and is now being found in man, mainly in countries which have a high pig farm MRSA prevalence e.g. The Netherlands, Germany, Spain and Italy. Pig farmers in Germany can be highly infected (**83%**) but, generally, the infection has remained in farmers and their family members (**4.3%**) and has not spread, to any major extent, into the general public in contact with them, such as schools (Cuny *et al.,* 2009). Swine veterinarians (**36%**), their laboratory staff and abattoir workers (**14%**) were also shown to have a higher incidence of infection than the national average (**1-2%**) in Germany (Blaha *et al.,* 2009). In Denmark, there has been an increase in cases of MRSA in man. Cases here refer to colonisation and clinical infections (see Figure 1).

Table 2 – *Human bacterial infections and potential swine association (Prescott et al., 2005; Mossad, 2010; Foxman, 2002)*

Human bacterial infections	Information	Potentially swine associated
Airborne/respiratory	39 million URTI cases/year US; 75% receive antibiotic prescriptions	
LRT infections (pneumonias)		
Corynebacterium diphtheriae	<100 cases in US/year	
Legionella pneumophila	1,000-1,400 cases/year US; 30,000 undiagnosed	
Bordetella pertussis	5,000 cases, 10 deaths/year US; 500,000 deaths WW	
Streptococcus pyogenes	Man asymptomatic carrier	
Streptococcus pneumoniae	Asymptomatic carrier; **60-80%** of pneumonias; 150-300,000 cases, 13-66,000 deaths in US	
Haemophilus influenzae		
Mycobacterium tuberculosis	WW 1 billion infected, 10 million cases/year, 3 million deaths; US 26,000 cases, 12,000 deaths/year	
Mycoplasma pneumoniae	Mortality <1%	
Chlamydia pneumoniae		
Meningitis		
Streptococcus pneumoniae		
Neisseria meningitidis		
Haemophilus influenzae		
Group B streptococci		
Listeria monocytogenes		
Mycobacterium tuberculosis		
Nocardia asteroides		
Staphylococcus aureus		Yes
Staphylococcus epidermidis		
Arthropod-borne infections		
Borrelia burgdorferi	20,000 cases/year US	
Yersinia pestis	25 cases 15% deaths US	
Direct contact diseases		
Bacillus anthracis	<1 case/year US; 20-100,000 cases WW	Yes
Clostridial infections		
Mycobacterium leprae	4,000 cases 2-300 new/year US; 14 million WW	
Sexually transmitted	8-10 million/year US	
Neisseria gonorrhoeae	Most common US	
Treponema pallidum		
Gardnerella vaginalis		
Haemophilus ducreyi		
Chlamydia trachomatis		
Mycoplasma genitalium		
Mycoplasma hominis	Widespread	
Ureaplasma urealyticum	Widespread	
Urinary tract infections (UTI)	8 million case/year US; women 14 times more often than men; >1 million catheter-associated UTI in hospitals and care homes	
Food and water borne		
Staphylococcus aureus		Yes
Bacillus cereus		
Clostridium perfringens		Yes
Clostridium difficile		Yes
Clostridium botulinum	<100 cases/year US	
Escherichia coli		Yes
Vibrio cholerae	<20 cases/year, <1% deaths US; 600,000 deaths/year WW	

Table 2 – *Cont...*

Human bacterial infections	Information	Potentially swine associated
Vibrio parahaemolyticus		
Shigella	25-30,000 cases/year US; 600,000 deaths/year WW	
Salmonella typhi	4-500 cases/year, <1% mortality US	
Salmonella spp	45,000 cases reported/year US; suspect 2-3 million	Yes
Campylobacter jejuni	2 million case/year US	
Campylobacter coli	10% human cases	Yes
Yersinia enterocolitica		Yes
Listeria monocytogenes		
Nosocomial (hospital)		
Staphylococcus aureus	LRT, surgical wounds, skin, bacteraemia	Yes
Escherichia coli	UTI, surgical wounds, skin,	Yes
Pseudomonas aeruginosa	UTI, LRT, surgical wounds, skin, bacteraemia	
Enterococcus spp	UTI, surgical wounds, bacteraemia	Yes
Enterobacter spp	UTI, LRT, surgical wounds, bacteraemia	
Acinetobacter spp	LRT	
Klebsiella pneumoniae	LRT	

Key – *WW – Worldwide; LRT – lower respiratory tract infection; URTI – upper respiratory tract infection; UTI – urinary tract infection; US – United States*

Table 3 – *The percentage incidence of infection and mortality of some human diseases on a population basis*

Infection	Incidence (population %)	Mortality (cases %)	Pig associated
Respiratory			
URTI	13 pa (75% treated = 9.75) (US)		
LRTI (pneumonias)	0.13 (US)		
S. pneumoniae	0.05-0.1 pa (US)	8.7-22.0 (US)	
Sexually transmitted	2.6-3.3 pa (US)		
Urinary tract infections (UTI)	2.7 (US)		
Food & water borne	0.76 (US)		
S. typhi	0.0017 pa (US)	<1.0 (US)	
Salmonella spp	0.015 reported; est 1.0 pa (US)		Yes
C. jejuni	0.67 pa (US)	0.005pa (US)	
C. coli	0.07 pa (US)		Yes

Key – *Populations – US 300 million; pa – per annum*

Table 4 – *Comparison of the likelihood of bacterial agents causing disease and causing resistance issues*

Bacterium	Colonisation	Infection	Disease	Death	Resistance
S. aureus (MRSA CC398)	Yes (DK) No (UK)	Yes (DK) No (UK)	Yes (DK) No (UK)	? No	Yes No
S. suis	Yes	Yes	Yes	Yes	No (penicillin Sens)
B. anthracis	Poss?	Poss?	Poss?	Poss?	No (penicillin Sens)
C. perfringens	Poss?	Poss?	Poss?	Poss?	No (penicillin Sens)
C. difficile	Poss?	Poss?	Poss?	Poss?	Poss? (nosocomial)
A. baumannii	Poss?	Poss?	Poss?	Poss?	Poss? (nosocomial)
E. coli	Poss?	Poss?	Poss?	Poss?	Poss? (nosocomial)
Salmonella spp	Yes	Yes	Yes	Yes?	Yes
C. coli	Poss?	Poss?	Poss?	Poss?	Poss?
Enterococcus spp	Poss?	Poss?	Poss?	Poss?	Poss?
Y. enterocolitica	Poss?	Poss?	Poss?	Poss?	Poss?

Key: Poss? – possible; penicillin Sens – penicillin sensitive

Figure 1 – *No of MRSA cases in man in Denmark (colonisation + infection) (Danmap, 2010, 2011)*

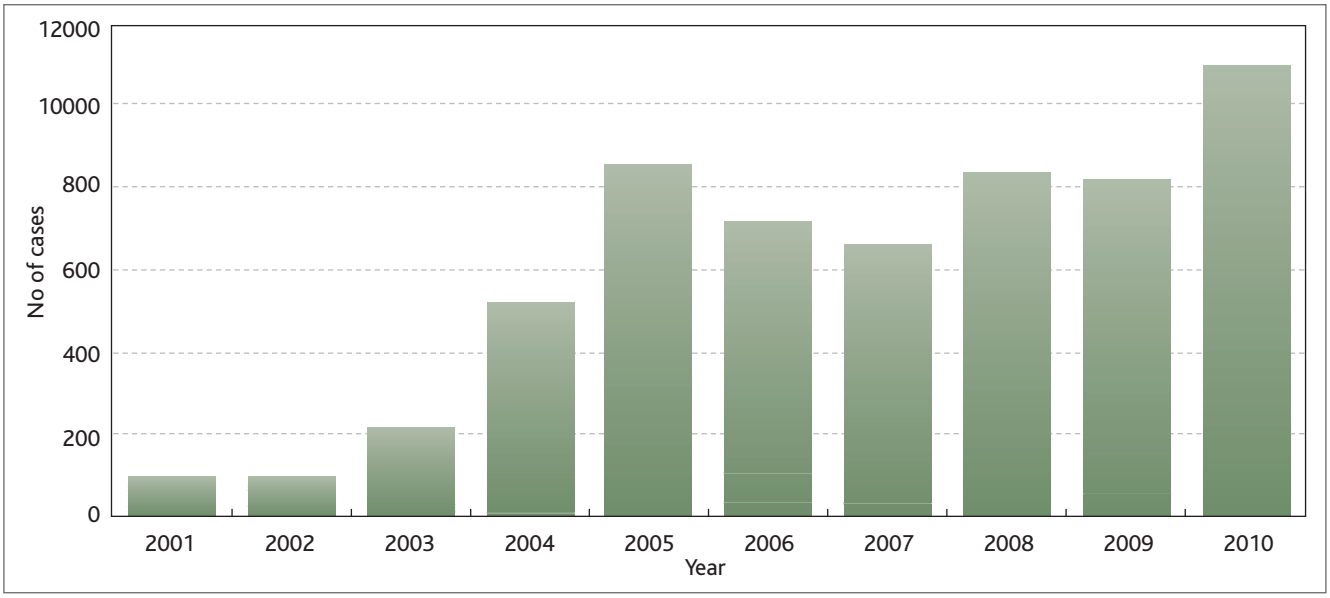
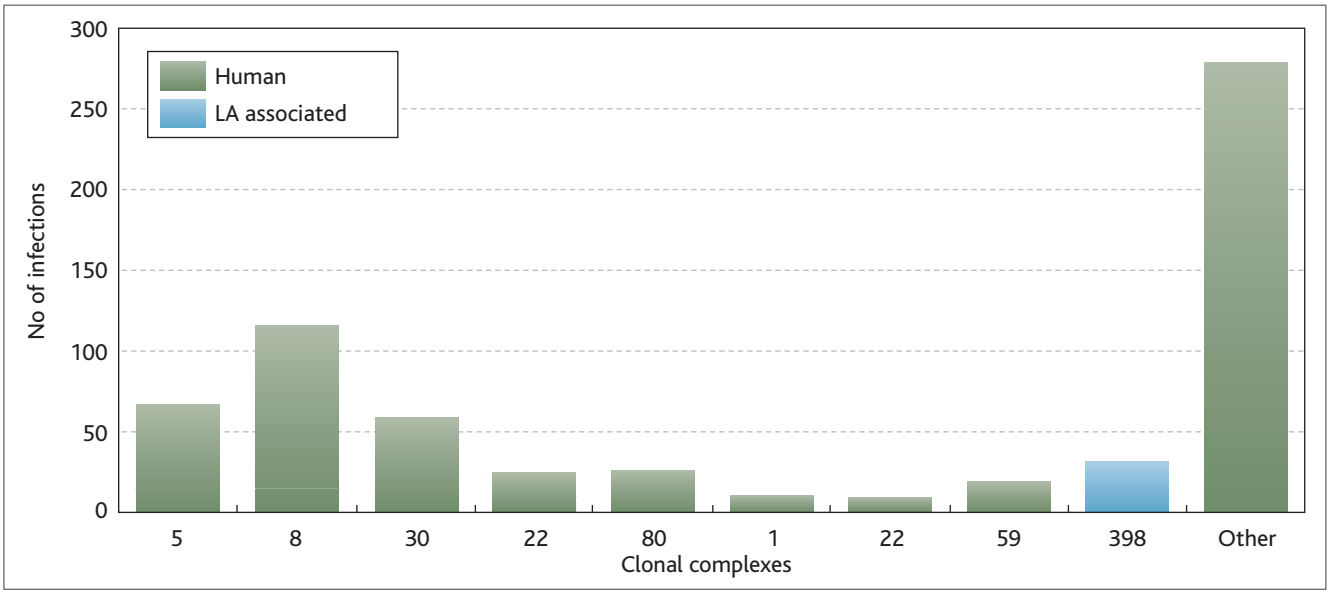


Figure 2 – *Common clonal complexes of MRSA causing clinical infections in man in Denmark in 2010 (Danmap, 2010, 2011)*



Approximately **4.95%** of 646 human MRSA clinical infections were associated with CC398, the livestock associated (LA) clone in 2010 (see Figure 2). Asymptomatic carriers were higher at 1**3.53%** of 451 isolates (Danmap 2010, 2011)

Overall, MRSA CC398 played a **9.57%** role in a rapidly growing problem in Denmark, where MRSA new cases (both infected and only colonised) increased from approximately 100 in 2001 to 1,097 in 2010 (11-fold increase). This has led to a voluntary suspension of use of third and fourth generation cephalosporins in veterinary medicine in 2010 and the implementation of a number of other controls to reduce antimicrobial use. On a population basis (5.5 million), MRSA cases were **0.02%** in Denmark and LA MRSA cases account for **0.002%**.

In spite of the UK being free of LA MRSA in pigs, the Health Protection Agency (HPA) reported that it has gone through a major MRSA epidemic but this was linked primarily to the medical arena and poor hospital hygiene practices (see Figure 3).

The introduction of hospital hygiene initiatives has resulted in a dramatic fall (-85%) in the incidence of MRSA bacteraemia cases in the UK from **0.012%** of population down to **0.0018%.** This highlights the major nosocomial impact of clinical MRSA infections in man, in comparison with LA MRSA associated transmission.

Figure 3 – *MRSA epidemic of bacteraemia cases in UK (HPA, 2006, 2012)*

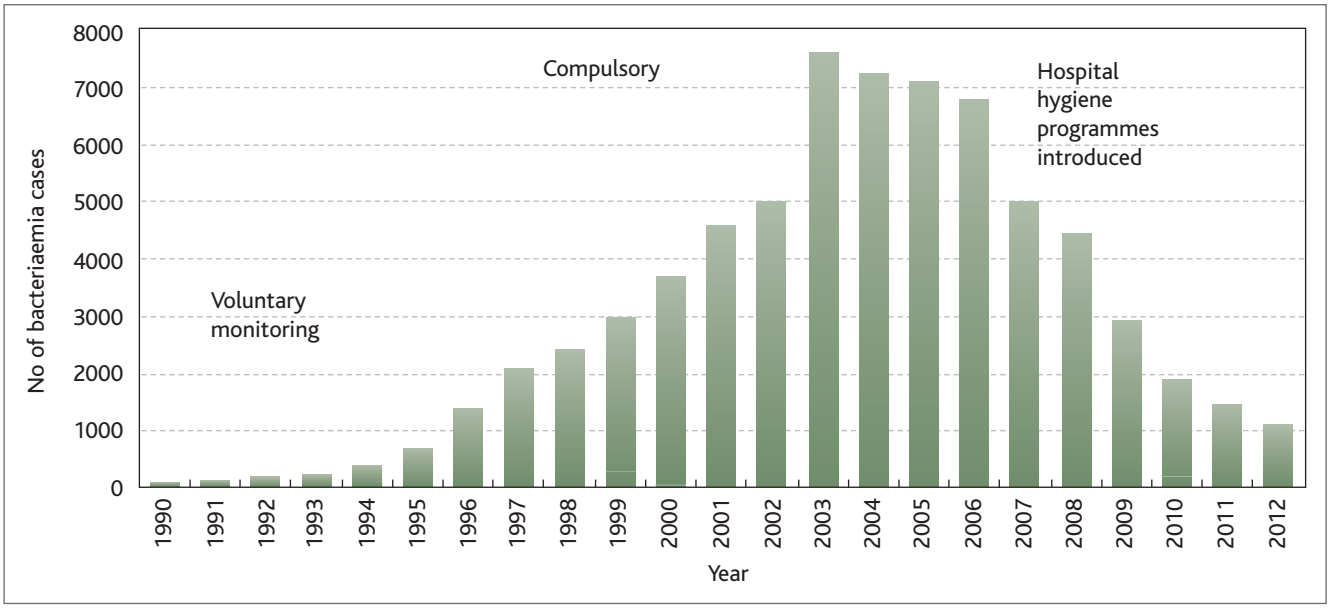
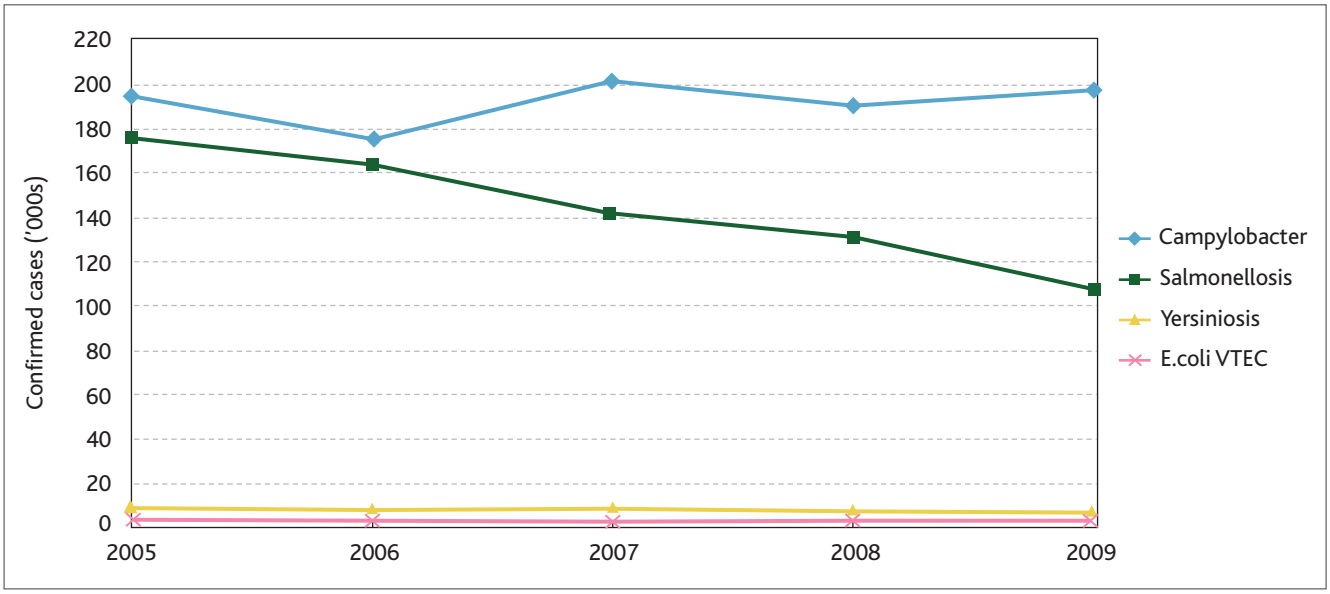


Figure 4 – *Incidence of confirmed cases of zoonotic and food-borne infections in humans 2005-09 (EFSA, 2011b)*



Zoonotic and food-borne outbreaks (EFSA, 2011b)

EFSA (2011b) reported on the incidence of confirmed cases of various zoonotic and food-borne infections in humans from 2005-09 (see Figure 4).

Campylobacter infections have remained fairly steady over the five year period but there has been a steady fall in Salmonella cases. *Yersinia* spp and *Escherichia coli (E. coli)* VTEC cases were comparatively low by comparison and will not be dealt with further.

Campylobacter spp infections

Burch (2002), reviewed the likely transmission of *Campylobacter coli* (*C. coli*) from pigs to man. The majority of isolates in man was *Campylobacter jejuni* (*C. jejuni*) (92%) and *C. coli* (8%). This was in contrast to the findings in pigs (see Table 5).

Generally, it was assumed that chickens/chicken meat were the main route of transmission of *C. jejuni* to man, as there was a high incidence of carcase contamination but pigs were still considered the main source of *C. coli*. EFSA (2011a), showed that 31% of broiler carcasses and meat were contaminated with *Campylobacter* spp but only 0.6% of pig meat. In addition, the species relationships in man were in complete contrast and were similar to chicken isolates.

Table 5 – *The isolation incidence (%) of Campylobacter spp from humans and animals (Burch, 2002)*

Species	*C. jejuni* (%)	*C. coli* (%)
Humans	92	8
Chicken	90	10
Cattle	99	1
Pigs	4	96

Table 6 – *Comparison of erythromycin (macrolide) resistance in Campylobacter spp from different animal sources (Burch, 2002)*

Species	*C. jejuni* (%)	*C. coli* (%)
Humans	2	15
Chicken	4	15
Cattle	1	–
Pigs	35	57

Table 7 – *Main Salmonella serovars found in humans in the UK between 2001-2011*

Year	2001	2006	2011
No of cases reported	18,063	13,412 (-25.6%)	8,937 (-50.4%)
Main serovar			
Enteritidis	65.1	55.3	30.4
Typhimurium*	13.0	12.1	25.9 (*+monophasic)
Virchov	2.2	3.2	1.5
Hadar	1.5	<0.7	<1.0
Newport	1.0	1.8	2.0
Infantis	1.0	1.2	1.9
Braenderup	0.9	0.7	<1.0
Agona	0.8	<0.7	1.6
Paratyphi B var Java	0.7	<0.7	1.3
Stanley	0.6	1.2	<1.0
Others	13.2	23.8	35.2

At that time (Burch, 2002), the macrolide tylosin was still extensively used in pigs and there was a relatively high level of resistance reported to erythromycin, another macrolide. The erythromycin resistance pattern was then compared to see whether a link or assessment of transmission of *C. coli* to humans could be estimated (see Table 6).

As the *C. coli* erythromycin-resistance profiles in pigs were completely different to those found in humans but were almost identical to chickens, it was considered that the contribution of infection from *C. coli* in pigs was probably very low, possibly **zero**.

This assumes that all infections are meat transmitted. The main incidence of campylobacteriosis in man increases in the summer months, so it was thought that barbecues might have an impact. Other sources might also contribute, such as swimming and beach holidays. In the United States (US), wildfowl such as Canadian geese (52%) were excretors of *C. jejuni* as well as Mallard ducks (40%) (Fallacra *et al.*, 2001), so fresh water swimming may also be an issue. Picnicking near cattle might also be a problem, as well as on the beach. Dingle *et al.* (2002), showed that *C. jejuni* found in beach sand was identical to human strains. Could this arise from sewage release into the sea?

Salmonella spp infections

In the UK, there have been many changes in the incidence of Salmonella infections in man over the last decade (VLA, 2002; VLA, 2007; AHVLA, 2012) (see Table 7).

The number of reported human cases has fallen by 50.4%, a substantial fall. There has been a dramatic fall in cases of *Salmonella Enteritidis* (*S. Enteritidis*) from 11,747 to 2,720 (-76.8%). *Salmonella Enteritidis* was primarily found in chickens and eggs, but with the European Food Safety Authority (EFSA) and the poultry industries' initiatives to reduce the incidence in poultry by vaccination of breeding hens and monitoring of flocks, this has fallen substantially. It must be remembered that cases picked up while travelling abroad are also included. In contrast, *Salmonella Typhimurium* (*S. Typhimurium*), the more pig associated bacterium, has increased in percentage terms but in case terms has stayed approximately the same at 2,340 in 2001 and 2,315 in 2011. On this basis, the incidence of Salmonella infections in reported cases in humans in the UK is **0.014%**, *S. Enteritidis* is **0.0043%** and the incidence of *S. Typhimurium* cases is **0.0037%**.

It is very hard to apportion responsibility for different species of animal's serovars that contribute to the incidence of disease in man. It is unfortunate that the incidence of monophasics in man is not recorded separately, as this would also add to the epidemiological knowledge of transmission. Pigs do carry a lot of *S. Typhimurium* (75.3% of isolates) and therefore has always been considered responsible for the bulk of transmission, yet poultry and cattle are also carriers. (see Table 8).

The Animal Health and Veterinary Laboratories Agency (AHVLA) (2012), further subdivided the *S. Typhimurium* serovars into phage types (PTs) (see Table 9).

Table 8 – *Comparison of the major Salmonella serovars found in humans and animals in 2011 (AHVLA, 2012)*

Human	Cases (%)	Pigs	Cases (%)	Chickens	Cases (%)	Cattle	Cases (%)
Enteritidis	30.4	Typhimurium	42.3	Montevideo	21.0	Dublin	65.0
Typhimurium*	25.9	4,5,12:i:-	22.0	Kedougou	19.3	Mbandaka	12.9
Newport	2.0	4,12,:i:-	11.0	Senftenberg	11.7	Typhimurium	7.3
Infantis	1.9	Derby	7.1	Livingstone	10.2	4,5,12:i:-	3.8
Montevideo	1.9	Bovismorbificans	3.3	Mbandaka	9.5	Montevideo	3.5
Agona	1.6	Kedougou	2.2	Ohio	7.1	Anatum	1.7
Kentucky	1.5	London	2.2	Typhimurium	2.9	Agama	0.8
Virchow	1.5	Newport	2.2	Enteritidis	2.0	Enteritidis	0.8
Paratyphi B var Java	1.3	Panama	2.2	Derby	1.5	4,12:i:-	0.6
Oranienburg	1.1			Thompson	1.2	Infantis	0.4
Others	30.7	Others	5.5	Others	13.7	Others	3.1

Key – **Typhimurium + monophasics; Pigs – 75.3% isolates; Cattle – 11.7%*

Table 9 – *Phage types (PT) of S. Typhimurium from humans and different animal species (AHVLA, 2012)*

Human	PT %	Pigs	PT %	Chickens	PT %	Cattle	PT %
DT193	28.6	U288	37.7	DT40	16.7	**DT104**	32.7
DT120	14.1	**DT193**	22.1	**DT193**	16.7	**DT193**	19.2
DT104	7.5	**DT120**	14.3	UNTY	16.7	**DT120**	11.5
DT8	5.4	U302	7.8			U302	9.6
RDNC	4.1	UNTY	6.5			DT8	5.8
U320	2.9	DT104B	3.9			DT2	3.8
DT191a	2.4					DT12	3.8
DT104b	2.1					U289	3.8
U323	1.9					UNTY	3.8
Others	31	Others	7.8	Others	50	Others	5.8
Human top 4 total	**55.6**		**36.4**		**16.7**		**69.2**
Est. proportional contribution (%)	**55.6**		**28.4**		**8.2**		**28.7**

It is possible that pigs only account for **28.4%** of the major *S. Typhimurium* infections in man or **7.4%** of Salmonella cases or **0.0011%** on a population basis in 2011.

The resistance profiles were examined for critically important antibiotics like the fluoroquinolones and third and fourth generation cephalosporins in the UK. There was no resistance to cefotaxime or ceftazidime (both 3G) or amoxicillin/clavulanic acid by *S. Typhimurium* but there was surprisingly in four isolates of *Salmonella Derby* (*S. Derby*). There was no ciprofloxacin resistance or amikacin resistance but there was 23% apramycin/gentamicin resistance mainly in the new monophasic Salmonella. Resistance to the critical antimicrobials is relatively low in the UK and, therefore, treatment failures due to resistance are also likely to be very low.

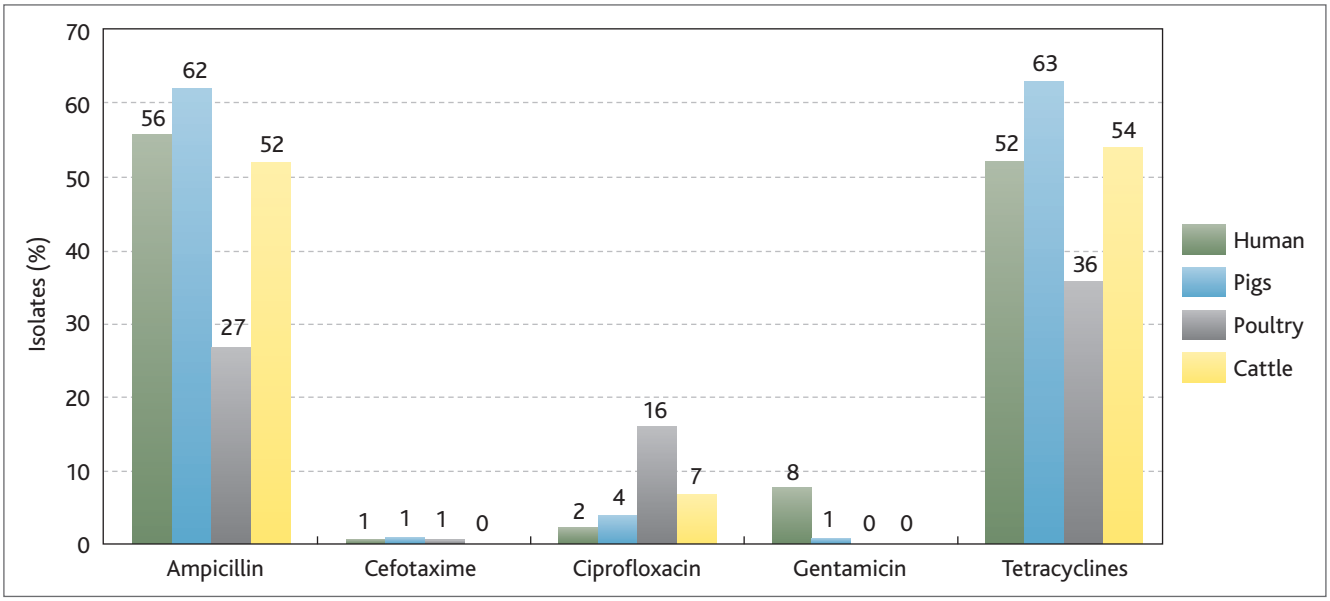
In Europe EFSA, 2011c reported on the comparative resistance of *S. Typhimurium* isolates from humans, pigs, cattle and poultry in 2009 (see Figure 5.)

There is some variation in the resistance profiles between animal and human species. None fit precisely but pig and cattle are more similar than poultry, except for gentamicin, where human resistance is comparatively high. Critical antibiotic resistance, say the fluoroquinolones (**4%**), from porcine *S. Typhimurium* might only account for **0.000044%** of resistance on a population basis and 3G cephalosporins (**1%**) even less at **0.000011%.**

Escherichia coli infections

From a public health point of view, *E. coli* VTEC isolates are the most significant with O157 serotype accounting for 51.7% of strains in 2009 (EFSA, 2011c). The main sources identified were mainly from meat from cattle (2.3% of samples) raw milk and sheep meat (3.2%). There is a high summer incidence and children are most commonly affected. Pig meat does not appear to be involved.

Figure 5 – *Comparative EU resistance profiles of various antimicrobials in S. Typhimurium isolates from humans, pigs and poultry (EFSA, 2011c)*



Transmission of *E. coli* to pig farmers was investigated by Nijsten *et al.* (1996) in the Netherlands (see Table 10). They found that antibiotic resistance of *E. coli* isolates in faecal samples of pig farmers was significantly lower than samples obtained from pigs. The resistance patterns of only **4%** of farmer *E. coli* were the same as pigs from the same farm. In many ways, this is surprising, as one would have expected a high direct exposure over a prolonged period, although via the faecal/oral route, would have caused a much higher colonisation/contamination rate, especially in comparison with the high MRSA colonisation rate seen in Dutch farmers via the nasal route.

This suggests that pig *E. coli* may not be able to colonise the intact human gut that well, with all its defence mechanisms (e.g. stomach acid, competitive and host-adapted gut flora). The result of failed colonisation did not appear to contribute greatly to antimicrobial resistance either. Any impact on pig-meat consumers can be considered much less in comparison with pig farmers but this has not been quantified.

In the Veterinary Medicines Directorate (VMD) (2010) they compared the antimicrobial susceptibility of UK *E. coli* causing bacteraemia in humans with clinical submissions for pigs and chickens (see Table 11).

The first observation is the difference in antimicrobial drugs that are used for testing between human and animal use. Ampicillin/amoxycillin demonstrate high resistance in both humans and animals, but when combined with the beta-lactamase inhibitor, clavulanic acid, the resistance falls dramatically in animals but not in humans, where there appears to be a 20% resistance. All the cephalosporins are third generation, and, again it demonstrates a very low level of resistance in pigs and chickens in comparison with human isolates. Not all of these resistant isolates will be carrying the ESBL resistant genes but they have been found in 9.2% of human cephalosporin-resistant *E. coli* and in animals – mainly in cattle isolates but once in chicken isolates. Fluoroquinolone resistance is also lower in animal medicine in comparison with human medicine. Aminoglycoside resistance is similar in both man and pigs at about 9-10% and trimethoprim (+ sulphas) are also high in man and pigs in comparison with chickens.

Overall, the data suggests that the transference of *E. coli* to consumers by meat is relatively low, the transfer of resistance can also be considered low and the impact on the use of antibiotics in human medicine has the main impact on human antimicrobial resistance.

Enterococcus spp infections

It is difficult to obtain precise data about the colonisation of the human gut by *Enterococci* from animals. Danmap 2006 (2007), offers some insight as they compare the resistance profiles of *Enterococcus faecium* (*E. faecium*) and *Enterococcus faecalis* (*E. faecalis*) from pigs, broilers and turkeys and healthy humans (see Table 12).

The resistance profiles of *E. faecium* in humans were very different to those found in pigs and broilers, especially with regard to tetracycline, ampicillin (converse), erythromycin, kanamycin and streptomycin. A maximum of **13%** using tetracycline could be transmitted but unfortunately, the precise profiles for each isolate were not compared.

Table 10 – *Comparison of pig and pig farmer E. coli antimicrobial resistance profiles (Nijsten et al, 1996)*

Antimicrobial	Pig resistance (%)	Pig farmer resistance (%)
Amoxicillin	25	28
Amoxicillin/clavulanate	0	0
Apramycin	0	0
Chloramphenicol	13	7*
Nitrofurantoin	8	3*
Nalidixic acid	0	2
Neomycin	7	3
Oxytetracycline	57	32*
Streptomycin	71	35*
Sulphamethoxazole	45	35*
Trimethoprim	16	10

Key – * – *p=<0.05*

Table 12 – *Comparison of resistance profiles in E. faecium from healthy humans, pigs and broilers (Danmap, 2007)*

Antimicrobial	Humans	Pigs	Broilers
Tetracycline	8	**61**	7
Ampicillin	**4**	0	0
Erythromycin	8	34	29
Gentamicin	0	0	0
Kanamycin	13	25	0
Streptomycin	4	30	14
Vancomycin	0	3	0*
Quinupristin/ dalfopristin	0	1	1

Key – **Using selective media vancomycin resistant E. faecium was found in 47% of broiler samples but not in pig and cattle (Danmap, 2011)*

The differences in *E. faecalis* resistance profiles were less marked, but again they were quite different. Individual isolate profiles were not compared thus a likely percentage figure could not be determined (see Table 13).

Considering that the bacterium needs to be transmitted via pig meat, which is sometimes eaten raw in Denmark but usually cooked or cured, the resistance profile would suggest a low colonisation rate and low resistance transfer rate to healthy humans of **18%** maximum from pigs, using erythromycin as a marker. Individual isolate resistance profile was not compared.

Other bacteria

With other bacteria, such as *Clostridium difficile*, the types found in animals (pigs, cattle and broilers) and human clinical cases could not be directly compared since the human isolates were selected for typing based on the O27 ribotype by PCR and also moxifloxacin resistance (Danmap, 2011). The O78 ribotype, which has been found in human cases, was found in cattle and pig isolates but were moxifloxacin sensitive. *Acinetobacter baumanii* isolates from human nosocomial infections were shown not to be derived from animal isolates using PFGE profiles (Hamouda *et al.*, 2011).

Table 11 – *Comparison of human and animal clinical E. coli isolates and their resistance (%) (VMD, 2010)*

Antimicrobial	Human (n=>10,000 isolates)	Pig (n=73-231 isolates)	Chicken (n=68-71 isolates)
Ampicillin	61	46	44
Amoxycillin/ clavulanic acid	**20**	**1**	–
Cefpodoxime (3rd gen)	–	1	1
Ceftazidime (3rd gen)	11	–	–
Cefotaxime (3rd gen)	12	–	–
Enrofloxacin/ Ciprofloxacin	23	6	6
Neomycin	–	9	3
Apramycin	–	10	1
Gentamicin	9	–	–
Tetracycline	–	78	51
Trimethoprim (sulpha)	40	53	24
Piperacillin/ Tazobactam	8	–	–

Table 13 – *Comparison of resistance profiles in E. faecalis from healthy humans, pigs and broilers (Danmap, 2007)*

Antimicrobial	Humans	Pigs	Broilers
Tetracycline	39	85	27
Ampicillin	0	0	0
Erythromycin	7	38	20
Gentamicin	0	**4***	0
Kanamycin	10	23	0
Streptomycin	10	32	0
Vancomycin	0	0	0

Key – **Potential reservoir/association with human gentamicin-resistant endocarditis MLST type ST16 (Danmap, 2011) or primarily nosocomial/hospital problem not determined*

CONCLUSIONS

If one compares the estimated disease incidence caused by pigs, transmitted to man, it can be seen to be relatively small and can be calculated as **0.003103%** on a population basis (see Table 14).

If the disease incidence caused by pigs is compared with infections in man, which are likely to be treated with antibiotics and, in their own right, select for resistance the proportion due to use in pigs can be considered minimal almost inconsequential (see Table 15).

Table 14 – *Overview of potential infection transmission to humans from pigs*

	Zoonotic infections			
Organism	*S. suis*	MRSA	*C. coli*	*S. Typhimurium*
Source	Pig	Pig	Pig	Pig
Host	Farmer/Man	Farmer/Man	Man	Man
Route	Respiratory/wound	Respiratory	Food/meat	Food/meat
Host susceptibility	Moderate	High	High	High
Colonisation	Low, 21% Farmer/ V. low man	High >83% Farmer/ 9.57% cases/ V. low man	No	Yes 25.9% cases
Infection	Very low	Moderate 4.94%	No	Moderate 7.4%
Disease incidence	**0.000003%**	**0.002%**	**0%**	**0.0011%**
Resistance transfer	No	No	No	Yes, potential
Mortality incidence	12.5%	No	No	Low
Treatment failure incidence	No	No	No	Low
	Commensal infections			
Organism	*E. coli*	*Enterococci*	*C. difficile*	*A. baumannii*
Source	Pig	Pig	Pig	Pig
Host	Farmer/Man	Man	Man	Man
Route	F/O; Food/meat	Food/meat	Food/meat	Food/meat
Host susceptibility	Low, 4% Farmer	Undefined	Undefined	Undefined
Colonisation	Low undefined	Undefined	Undefined	Undefined
Infection	No (commensal)	No (commensal)	No (nosocomial)	No (nosocomial)
Disease incidence	No (commensal)	No (commensal)	No	No
Resistance transfer	Yes potential	Yes potential	No	No
Mortality incidence	No (commensal)	No (commensal)	No	No
Treatment failure incidence	Very low undefined	Very low undefined	No	No

Key – *F/O – Faecal/oral*

Table 15 – *Relative case and resistance transmission from pigs to humans*

Pig transmission	Transmission (%) on a population basis	Human infections	Population affected and treated (%)
S. suis	**0.000003**	Respiratory (URTI & LRTI)	**9.88**
MRSA	**0.002**	Sexually transmitted	2.6-3.3 (say 3.0)
Campylobacter spp	**0.0**	Urinary tract	**2.7**
S. Typhimurium	**0.0011**	Food and water borne	**0.76**
Total	**0.003103**	**Total**	**16.34**
	Transmission on a case basis		
Cases/100,000 population	**3.1**		**16,340**
Case potentially transmitted from pigs to man	**0.019%**		**100%**
Resistance transmission of critical antibiotics (at 2%)	**0.00034%**		**100%**

If the disease incidence in humans associated with bacteria from pigs at **0.003103%** on a population basis is compared with human infections of **16.34%** on a population basis per year, which are likely to be treated with antimicrobials, the percentage of infections potentially caused by pigs is approximately **0.019%** of human infections. If all the bacteria coming from pig infections were resistant, it would only contribute **0.019%** of resistance to humans. The resistance rate of 'critically important' antimicrobials is about **2% (0-6%)**, then contribution to human resistance is likely to be about **0.00034% (0.0-0.001%)**, which is a remarkably small amount. That is why antimicrobial resistance in pigs is not so important for public health, in comparison with the amount of resistance that human doctors directly produce, especially in the hospital situation.

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