"Healthy pig for a healthy life"

The role of medicines and vaccines

David G S Burch, Octagon Services Ltd, Old Windsor, Berkshire, UK

Introduction

There have been some major changes in pig production over the last 40 years, from mainly small family units to massive industrial scale production. As a result there has been a necessary intensification of production and with each step there has been a move to more efficient production and feed utilization. Often, as a consequence, it has put more pressure on a pig, usually resulting in an exacerbation of an existing disease or a new disease developing. In the seventies, progressive atrophic rhinitis was common, usually as a result of merging two herds to rapidly expand production; one herd carried the right *Bordetella bronchiseptica* and the other the right dermonecrotoxin-producing *Pasteurella multocida* type D, resulting in the development of the disease. The buying in of large number of gilts from saddle-back breeder herds, which were commonly infected with swine dysentery (SD), resulted in most of the swill-fed herds in Berkshire being infected. The concepts of biosecurity and breeding herd health management were in their infancy then; Belgium, reportedly, has not learnt this lesson, even now, regarding SD.

Globalisation has also played a major role in the spread of diseases. With the requirement to improve the lean-meat producing genetics of herds there has been a steady spread of diseases either by live pigs or semen of such immuno-suppressive infections as porcine reproductive and respiratory syndrome (PRRS) virus and porcine circovirus type 2b (PCV2). Unfortunately for Asia, most of the infections in pigs have come from Europe and N. America but fortunately for us, Nipah virus did not spread from Malaysia, however avian influenza viruses (H5N1) have gone the other way.

All these changes, resulting in increased disease pressure, have encouraged changes in production systems to minimise disease spread, such as 3-site production, all-in, all-out systems but has also put pressure on the use of medicines, especially antibiotics, as front line control and resistance is emerging as the key issue in many areas. Fortunately, this disease pressure has resulted in the development of new vaccines to improve long-term disease management to produce a healthy pig.

The role of medicines

Antimicrobial use is still widespread and commonly applied and today is causing the most controversy. In the early days when antimicrobial resistance developed it was possible to switch to the next new one and continue using that until it was necessary to change again. Now, everything is changing, there are likely to be few or even no new molecules being developed in the foreseeable future.

There have been many changes to the antimicrobial use over recent years. Since 2006 antimicrobial growth promoters (GPs) have been finally removed from EU feeds. Thailand, Korea and Australia have followed. The original ban on antibiotic GPs (1999) under the 'precautionary principle', which were relevant in human medicine, such as avoparcin (vancomycin in man), virginiamycin (dalfopristin-quinupristin) and the macrolide, tylosin (erythromycin), resulted in an increased use of therapeutic antimicrobials, mainly the tetracyclines and the switching of tylosin to a therapeutic, under veterinary control. The banning of carbadox, olaquindox and salinomycin, which all had 'prophylactic' effects against SD and some other enteric infections, have resulted in the increased pressure on the therapeutic antimicrobials that are left, in particular, tiamulin, valnemulin,

click here for
- PIG ARTICLES INDEX -
www.octagon-services.co.uk/pigs.htm

lincomycin and tylosin and multi-resistance is starting to emerge in *Brachyspira hyodysenteriae* isolates, even against the pleuromutilins in some countries.

The recent discovery of methicillin-resistant *Staphylococcus aureus* (MRSA) in pigs, in many major pig producing countries in the EU, such as Netherlands, Germany, Spain and Italy, as well as in chickens and cattle, has created serious concern in regulators in the European Commission (DG Sanco) who are now reviewing the use of antimicrobials in general but especially 3rd and 4th generation cephalosporins, which are thought to be the main cause of the problem. This has opened up the debate again of how much antimicrobial resistance in man comes from animals. The fluoroquinolones are also under review again, as the two families of antimicrobial drugs are considered 'critical' in human medicine. Extended-spectrum beta lactamases (ESBLs) have been found in Gram-negative bacteria such as *Escherichia coli*, and these also confer resistance against 3rd and 4th generation cephalosporins and are of potential concern to human medicine, as the gene is transmissible via plasmids. The oral use of fluoroquinolones has already been attacked in the US and has been stopped in poultry, although recently permitted for use as an injectable for pigs but their use is not permitted in farm animals in Australia. There is also a move in the US to try to reduce the amount of antibiotics used by stopping their use for growth promotion and prevention. In the EU, some countries have introduced controls on the prescribing and dispensing of antibiotics to pigs (Denmark, Netherlands) and the Netherlands have called for a 50% reduction in use and the cessation of in-feed medication. In Asia, China has shown that antimicrobial resistance is a major problem (Lei et al, 2010) especially regarding fluoroquinolones and aminoglycosides (see Table 1).

Table 1. Comparison of *E. coli* antimicrobial resistance (%) from pigs in China (Lei et al, 2010) and Denmark (Danmap, 2004) both clinical and survey isolates

Antimicrobial	China (survey & clinical)	Denmark (survey)	Denmark (clinical)
Ampicillin	93	23 (BLs)	43 (BLs)
Amoxycillin/clavulanate	-	<1	4
Cefazolin (1st gen)	19	4	7
Ceftriaxone (3rd gen)	10 (ESBLs?)	0	0
Streptomycin	-	44	66
Neomycin/kanamycin	81	6	31
Apramycin/gentamicin	77	<1	9
Nalidixic acid	95	2	27
Ciprofloxacin	76	0	0
Tetracycline	98	31	73
Trimethoprim/Sulpha	91	14	36

Key: BLs – beta-lactamase enzyme resistance, neutralised by clavulanic acid; ESBLs – Extended spectrum beta lactamases, commonly associated with 3rd generation cephalosporin use (CTX genes)

Much of this drama in Europe is politically driven but there is no doubt, that we must rethink our strategic use of antimicrobial drugs, to use them more prudently and thereby prolong their efficacy and availability for veterinary use. With such regulatory uncertainty, the pharmaceutical industry is unlikely to invest and develop new molecules. Most of the research is coming from the human pharmaceutical side and if veterinary use is considered likely to have a damaging effect on human medicine, it is a further disincentive.

The perceived hazard of antimicrobial resistance spread from pigs to man is a relatively low risk for the consumer providing that the pork is cooked properly. However, there are some risks for people working with or slaughtering/processing pigs, as has been demonstrated by MRSA ST398 in the EU and *Streptococcus suis* in China. Salmonella, especially Typhimurium is a potential problem regarding food poisoning from pork but the Danes have shown that treatment of carcasses with heated steam

can substantially reduce the surface contamination and substantially reduce the risk of salmonella transfer and at the same time it will also reduce the potential transmission of antibiotic resistance.

High herd health is critical, but without good biosecurity and a degree of isolation, the farm is likely to break down with the local endemic diseases. High health and specific-pathogen free (SPF) pigs can save farms from using a lot of antibiotics, however. Eradication of enzootic (mycoplasmal) pneumonia (EP) and SD is achievable. *Actinobacillus pleuropneumoniae* is more difficult but *Streptococcus suis* has proven very difficult as piglets are infected by the sows in the first week of life. Purchases from reliable disease-free sources and quarantining of animals are essential to prevent the re-introduction of diseases.

Most herds are moderate health and therefore biosecurity is essential to minimise the importation of new diseases or new strains of diseases such as PRRSV. Closed herds seem to be unpopular these days because of the need for genetic improvement, but they were a good way of stabilising a herd's immunity and thereby reducing many problems. The use of antibiotics is likely to be more widespread in moderate health herds, so attempts to minimise their use to key stress times, such as weaning and moving would help, rather than a dependence on continuous use. There is a big debate about not using antibiotics for prevention but only for treatment. Each one has its role but 'early treatment' or metaphylaxis, is probably the most effective form of antibacterial use, as bacterial numbers are low in the animal and resistant mutant selection is therefore also likely to be low. Diagnostic testing is essential to determine what is present on the farm; culturing and bacterial sensitivity testing is helpful so that the right antibiotic is chosen for the right bug at the right dose. Don't keep throwing antibiotics at a problem, stand back and see what management practice, environmental problem or possibly if an immuno-compromising infection is causing the problem, e.g. *Mycoplasma hyopneumoniae*, PRRSV or PCV2 and in certain parts of Asia, swine fever and pseudorabies viruses.

Will other supportive therapies help? There has been progress in the use and understanding of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ketoprofen, to reduce the almost over-reaction of the body to fight disease. These used in drinking water concurrently with antibiotics may improve the pig's response to treatment and return its health more rapidly.

The role of vaccines

Great progress has been made over the last few decades with vaccines. For example, vaccines against PCV2 have made an outstanding contribution to pig health over recent years. Mortality figures have fallen nationally in the UK to pre-PCV2b epidemic levels, as a result. There are still some areas of confusion and misconceptions but basic vaccination principles appear to apply. There have been exciting developments in virology and vaccine production, demonstrated by the use of recombinant technology, by inserting the open-reading frame (ORF) 2 into a baculovirus system to produce the capsid-protein antigen and even a hybrid (PCV1/PCV2) virus was produced. They have a high level of efficacy of 92% (Martelli, 2010).

Great progress has also been made with adjuvants to stimulate an immune reaction. This was highlighted particularly with the development of *Mycoplasma hyopneumoniae* vaccines. The early vaccines did not necessarily give the optimum protection, usually with field infection lung-lesion improvements of <50%. The introduction of the oil-in-water and water-in-oil adjuvants increased efficacy to >60% in the field and in artificial challenge studies approaching 90%, as well as enabling the development and use of one-shot vaccines. Sub-unit (P97) mycoplasma vaccines have also shown comparable efficacy.

click here for
- PIG ARTICLES INDEX -
www.octagon-services.co.uk/pigs.htm

PRRSV vaccines have been less clear cut. The killed vaccines appeared to have minimal effect in spite of stimulating an antibody response. The live vaccines seemed to be effective in protecting the sows against reproductive and infertility problems but in the growing pig there is still some debate over the variability of response and their ultimate efficacy. The US strain MLV vaccine claim a 70% lung lesion reduction with a range of 17-97% in 16 trials (Roof et al, 2007). Genetic drift and even shift is thought to account for much of the problem, although current MLV vaccines are reported to be effective against the highly pathogenic strains appearing in Asia.

In general, vaccines used in sows give good protection to the sow and developing piglets as demonstrated by parvovirus and PCV2 vaccines. In addition, they will increase maternally derived antibodies (MDAs), which are passed onto the piglets via the colostrum. This offers early protection to the piglet but as the antibodies wane, and the piglets are exposed to infection they have to develop their own immunity. This may result in the pig's own immune response and seroconversion with or without expression of disease but this appears to depend on the level/severity of challenge and its timing in relation to its own immune response development. PCV2 piglet vaccines appear to give more reliable protection throughout the life of a growing pig, which is not really surprising.

The site of infection is also of major significance to vaccination. Is it in the gut or respiratory or reproductive tract on the mucosal surface; is it invasive causing bacteraemia or viraemia? In the case of PCV2, it causes a viraemia and therefore comes into direct contact with antibodies and the clinical disease can be controlled. With *M. hyopneumoniae*, the infection is on the mucosal/epithelial surface and the induced vaccinal antibody response is primarily systemic. There is an additional cell-mediated effect but the production of surface-acting antibodies (IgA) are not readily primed by the vaccine. In poultry, the modified-live, or temperature-sensitive live mycoplasma vaccines, which primarily colonise the upper respiratory tract do give a direct surface immune stimulation and offer possibly better protection.

Vaccines against other bacterial pathogens, such as *A. pleuropneumoniae, H. parasuis*, and *S. suis* have had a variable response to heterologous challenge, because of the range of serotypes found. Sub-unit vaccines and toxoids have been successfully developed for *A. pleuropneumoniae* based on the selection of cross-protective antigens such as outer membrane proteins (OMPs) and lipo-proteins (OMLPs) and Apx cytolysin exotoxins I, II & III, which cover 12 major serotypes (see Table 2). Whether it was the antigens alone or the combination with a powerful adjuvant, the vaccine proved cross-protective but originally resulted in frequent adverse effects in the pig.

Suitable sub-units have been examined to give cross-protection against *S. suis* and *H. parasuis* but to date they lack sufficient cross protection to heterologous serotypes.

The attraction of the development of cross-protective sub-unit vaccines is obvious but the potential then to develop multivalent vaccines to cover a range of infections with a single vaccine is also particularly exciting. Mixed vaccination with vaccines for PCV2 and *M. hyopneumoniae* using the same adjuvant is starting to take off now and even reconstituting with live PRRS vaccine in the US has been introduced, to reduce the number of vaccines administered.

click here for
- PIG ARTICLES INDEX -
www.octagon-services.co.uk/pigs.htm

Table 2. *A. pleuropneumoniae* serotypes in Asia, virulence and sub-unit cross protection (Burch unpublished data)

Serotype	1	2	3	4	5ab	6	7	8	9	10	11	12
Australia (%)	9	-	-	-	8	1	19	8	-	-	-	-*
New Zealand (%)	-	-	-	-	55	-	37	7	-	-	-	-
Korea (%)	-	53	-	-	25	20	2	-	-	-	-	-
Thailand	Y	Y	Y	-	Y	-	Y	-	-	-	-	-
Taiwan	Y	y	y	-	Y	-	y	y	-	-	-	-
Malaysia	Y	Y	-	-	Y	-	Y	Y	-	-	-	-
China	Y	-	Y	-	Y	-	Y	Y	-	-	-	-
Virulence	VV	V	V	-	VV	V	V	V	VV	VV	VV	v
Toxins/antigens/enzymes												
Apx I	Y	-	-	-	Y	-	-	-	Y	Y	Y	-
Apx II	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	Y	Y
Apx III	-	Y	Y	Y	-	Y	-	Y	-	-	Y	-
OMP (42kDa)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
OMLP (47kDa)	Y	Y	Y	Y	Y	-	Y	Y	Y	-	Y	Y
OMLP (48kDa)	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	-
Cysteine-Cysl 1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Transferrin – Tbp	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Key: Y = Yes; V = Virulent; VV = Very virulent; v = low virulence; * = 55% were other STs

In pigs, one of the major surface infection vaccines introduced has been the attenuated live *Lawsonia intracellularis* vaccine. The bacteria penetrate the mucosal surface cells, stimulating a local and systemic immune response but do not progress to full disease. The efficacy appears to be very good but administration timing is difficult, as many of the antibiotics commonly used in pig medicine, such as the tetracyclines, macrolides, lincosamides and pleuromutilins, also kill the vaccine.

Sub-unit vaccines, based on candidate antigens from 'reverse vaccinology', are being examined for *Brachyspira hyodysenteriae*. If successful, this would alleviate the pressure on the antibiotics directly, but developing sufficient protection at a mucosal level will be demanding for such a vaccine.

Conclusions

Advances in vaccination as well as improvements in herd health management have to be the way forward to improve pig health and productivity. Antibiotics are helpful as a frontline defence but continued, excessive dependence on their use will result in extensive antimicrobial resistance, and a lack of alternative controls to continue economic production. Farms with multi-resistant *B. hyodysenteriae* already have to slaughter out (depopulation) in the EU and multi-resistant *A. pleuropneumoniae* and *E. coli* are present in Asia and difficult to control. The chances of new families of antibiotics being developed for animal health are small as they are derived primarily from the human pharmaceutical industry, therefore the current products need to be preserved and used more prudently for veterinary medicine and the future pig's health.

click here for
- PIG ARTICLES INDEX -
www.octagon-services.co.uk/pigs.htm