WVPA Europe Meeting 2014

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The threat from Africa & Middle Eastern IB viruses

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Introduction

Infectious bronchitis is primarily a respiratory disease of chickens caused by the Type Three coronavirus, infectious bronchitis virus. In addition to affecting the respiratory tract, IB viruses cause important losses in egg production and quality in laying flocks and some types have a predilection for the kidneys where the resultant nephrosis can cause high mortality in young stock. The disease is worldwide and the virus exists in a large (and increasing) number of serotypes and nowadays genotypes, the latter ad hoc classification being based on the sequencing of the S1 spike gene. Genetic variation occurs constantly, principally through mutations and recombinations but only occasionally do new important types appear. New variants are described regularly in different countries. Some genotypes have wide distribution globally, while others appear localised in confined regions. The main approach to control is by the use of live and inactivated vaccines. However, cross-protection between types is usually poor and the continual appearance of new types challenges vaccination strategies and necessitates constant surveillance of IB viruses in circulation.

This paper considers the real or potential threats to European chicken flocks posed by the viruses present in two neighbouring regions, namely Africa and the Middle East.

The global situation with infectious bronchitis viruses

Disease caused by IB viruses is common wherever chickens are kept. Some strains such as Massachusetts, Arkansas and 4/91 (793B-type) are found worldwide while others are localised. Without question, the wide distribution of some of the well-established types has been due to the use of vaccines derived from them. However, in many other instances, the factors responsible for global spread or its absence is not clearly understood. For example, the QX type, first described in the 1990s in China has quickly spread to many parts of the world while other have not.

Interestingly, the USA does not have QX or any of the variants present in Europe, apart from American-derived vaccine types. Africa and South America

have some of the European types. Australia however has its own distinct types.
The precise roles played in IB virus spread by movement of stock, poultry products legally or otherwise are poorly understood. At the present time, there is no evidence that wild birds - although sometimes infected with or carriers of IBV-like viruses - are implicated in the long distance transmission of IB as are migratory waterfowl in the global spread of avian influenza or Newcastle disease.

Brief history of IBV types in Europe

The first IBV described in Europe was in 1948, the Massachusetts type having originated from the USA. This situation held until the 1970s and '80s when variant serotypes were described in Holland and UK, and later elsewhere. Cross-neutralisation in fertile eggs was the only means of comparison at that time and identification was a slow process. The variants were isolated from flocks vaccinated with Mass-type vaccines. Experimental data showed that that available Mass vaccines were not protective against these novel serotypes. Vaccines were prepared against some of these viruses and those against D274 and D1466 are still available.
The next milestone occurred in the early 1990s when two groups in UK described viruses of the same serotype, named separately, 793B and 4/91. They were isolated from vaccinated commercial stock and initially, behaved differently from conventional IBVs, with slower spread and associated with diarrhoea and pectoral myopathy. Commercial vaccines for this group were made available and are still widely used today. This group of viruses was soon reported to have spread to many countries in the world, apart from notably, USA and Australia. The origin of 793B-type viruses and the Dutch variants were unknown. However, by this time, molecular methods had been developed for speedy diagnosis (PCR) while comparison of the S1 spike gene sequences of viruses (now *genotypes*) could be made, allowing for a molecular basis for understanding IB epidemiology.
In the first decade of this century, two new genotypes appeared. The first, named Italy-02 proved difficult to grow in eggs and caused relatively mild disease. No new vaccine was developed since it was found that a combination of existing vaccines (Mass followed by 4/91 type) was efficacious. Again, work in Spain concluded that this was a new genotype of unknown origin. This virus spread widely throughout Europe but not significantly beyond.
QX IBV originated in China in the 1990s and arrived in Europe approximately six years later – a time interval strikingly similar to that taken by avian influenza

virus H5N1 via broadly the same route. How this long-distance transmission occurred is unclear but it is likely to have passed through the Middle East on its way to Europe.

In China, QX was originally described as being associated with proventriculitis but in Europe, it has had drastic effects on commercial flocks as a cause of nephrosis in young stock and the phenomenon of false layers, which prevents mature hens from laying due to oviduct damage after early infection. A live commercial vaccine is now available, although some groups have shown that application of the combination of Mass and different vaccines can be protective.

A recent report from Italy identified another Chinese-origin IBV, Q1 which is genetically different from QX. It was isolated from non-vaccinated broilers. It is uncertain if it arrived via the Middle East. Interestingly, it has been reported in South America.

Threats from IB viruses in North Africa

Potential threats from Africa are most likely to come from the countries Bordering the Mediterranean rather than sub-Saharan nations (although it should be remembered that turkey rhinotracheitis was first described in South Africa but soon appeared in Europe!). Morocco, Tunisia and Libya comprise this section. Egypt though geographically in North Africa, from the IB aspect, appears to have more in common with the Middle East and is referred to below. IB in Algeria the nature of IB types has not been reported.

The most notable IBV reported from North Africa has been Moroccan G, isolated in the mid-1980s and shown to have 96% S1 gene sequence identity with the 793B-4/91-Cr88 group but before the latter were reported in Europe. Evidence suggests that the Moroccan virus could have been the progenitor of the major 793b variant types. The geographic closeness of Morocco to Europe may have been a factor. In recent years, other unique strains have been isolated in Morocco and Tunisia but hitherto have offered no threat. In Libya, types found in Egypt and other Middle Eastern have recently been reported.

Threats from IB viruses in the Middle East

In recent years there has been much activity in reporting the prevalent genotypes in the region, which include vaccinal genotypes. Many are present in neighbouring countries but with some distinct regional types identified. Several of the viruses e.g. Israeli types IS/1494/06 and IS/885/00 are nephropathogenic. Experiences from elsewhere suggests that those virus with a particular predilection for the kidneys do not spread geographically in the

way that those with the more common respiratory predilection. An example is the European B1648 which appears to have remained in Europe.
Much recent experimental work in Egypt suggests that for several of the unique Middle Eastern IBVs, a combination of commercial available Mass and 793B-type vaccines offers satisfactory protection.

Conclusions

It is impossible to predict with any certainty, what threats are posed by IBV strains from Africa or the Middle East. The arrival of 793B types in the 1990s and in particular QX in the 2000s could not have been foreseen. In the same way, though there are countries with a number of unique IBV genotypes very close to Europe, it cannot be predicted if any of them represents a real threat to European poultry flocks.
The information about how IB viruses are able to be transmitted over long distances is notably lacking. At the present state of knowledge, we have no evidence that migratory birds play a part. In those instances where wild birds have been found to harbour IB viruses or IB – like coronaviruses, they have usually been found close to commercial flocks or the viruses have not been reported in commercial chickens.
In view of our lack of knowledge in this area, and the impossibility of predicting the arrival of new types from elsewhere, the importance of constant surveillance cannot be over emphasised, not only for recognising the appearance of novel types from elsewhere but also for identifying new variants which emerge through simple mutation or recombination of already present types. We are now in the fortunate position of having the sophisticated molecular methods to do these investigations.

Recommended reading

de Wit JJ, Cook JK, van der Heijden HM. (2011) Infectious bronchitis virus variants: a review of the history, current situation and control measures. *Avian Pathology* . 40: 223-35.

Jackwood MW. (2012) Review of infectious bronchitis virus around the world. *Avian Diseases*. 56: 634-41.

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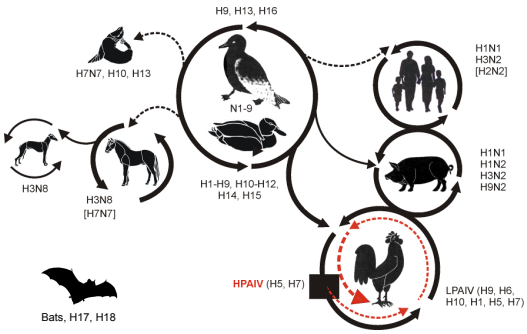
Professor C. Harder
OIE-FAO Ref. Laboratory for AI

Avian influenza developments & threats to Europe

Ecology of influenza A viruses



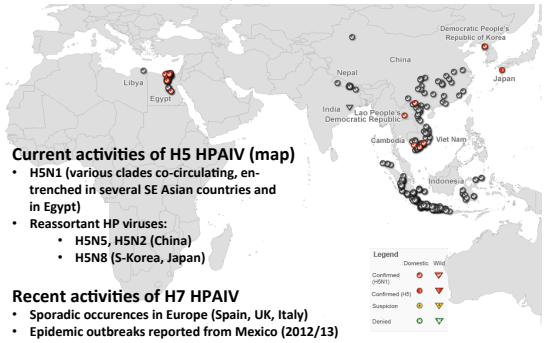
Threats of HPAIV

- In nature restricted to subtypes H5 and H7 (with various N partners)
- Molecularly defined pathogenicity marker (polybasic HA cleavage site)
- May arise spontaneously and unpredictably in poultry infected with low pathogenic AIVs of subtypes H5/H7
- High mortality in gallinaceous poultry (peracute deaths)
- Variable pathogenicity in water fowl („Troian“ ducks)
- Potentially zoonotic

Globally notifiable poultry disease

FRIEDRICH-LOEFFLER-INSTITUT since 1910 FLI Bundesforschungsinstitut für Tiergesundheit Federal Research Institute for Animal Health

FAO, EMPRESS, Update on Animal Influenza, No. 614



Current activities of H5 HPAIV (map)

- H5N1 (various clades co-circulating, entrenched in several SE Asian countries and in Egypt)
- Reassortant HP viruses:
  - H5N5, H5N2 (China)
  - H5N8 (S-Korea, Japan)

Recent activities of H7 HPAIV

- Sporadic occurences in Europe (Spain, UK, Italy)
- Epidemic outbreaks reported from Mexico (2012/13)

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Threats of LPAIV

- Notifiable (H5, H7) and non-notifiable (H9N2 and the rest) LPAIV (with various N partners)
- Molecularly defined pathogenicity marker for H5 and H7 (monobasic HA cleavage site)
- Low pathogenic AIVs of subtypes H5/H7 may become precursors of HP biotypes
- Variable, usually asymptomatic-low, pathogenicity (cave: co-pathogens, environmental factors)
- Potentially zoonotic

Notifiable poultry disease, if H5/H7

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Year	Subtype	Outbreaks	State/DE
2014	H5N1	1	NI
2013	H5N3	1	BW
	H5N2	1	TH
	H5N1	1	BB
	H7N7	2	NW
	H7N7	5	NI
2012	H5N2	2	HE
	H5N3	1	SH
2011	H7N7	23	NW, NI, SN, BW
2010	H7N7	1	NI
	H5N2	2	MV
2009	H7N7	1	NW
	H5N3	3	NI
	H5N2	1	TH
2008	H5N3	31	NI
	H5N1 HP	1	SN
	H5N8	2	SN
	H5N3	1	ST
2007	**H5N1 HP**	6	BY, BB, TH
	H5N2	1	NW
	H5Nx	1	BY
	H7N3	1	NW
	H7Nx	1	BY
2006	**H5N1 HP**	1	SN
	H5Nx	1	HE

Notifiable AI in poultry in Germany since 2006.

LPAIV dominate outbreaks of notifiable AI

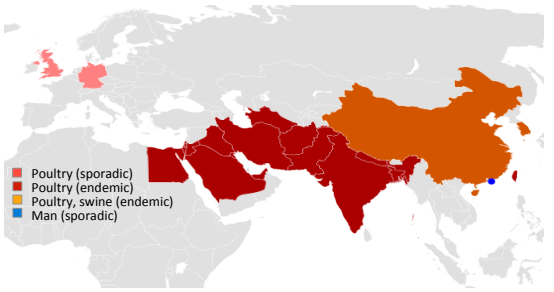
Prediction of „time-to-HP-mutation“ not possible!

Zoonotic potential is not dependent on pathotype

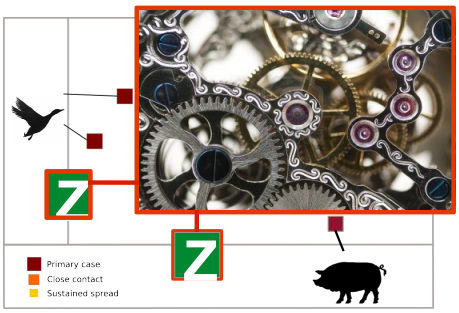
Limited possibilities to predict zoonotic potential.

How about AI that is non-notifiable (H9N2)?

Wide geographical spread of H9N2 infections in poultry



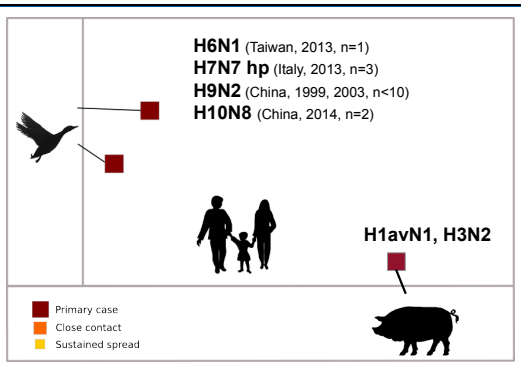
What renders animal influenza viruses zoonotic?

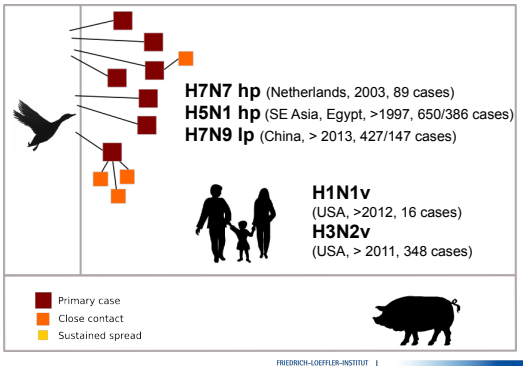


What renders animal influenza viruses zoonotic?

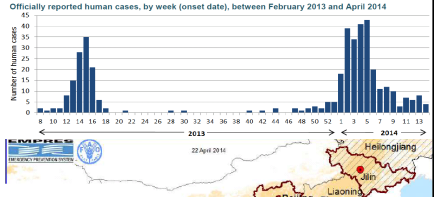
- Receptor usage (2-3 vs. 2-6, HA, NA) ?
- pH stability (endolysosomal escape, HA) ?
- Nuclear import machinery (all segments)
- Replication efficacy (body temperature! 40 vs 36°C; PB2)
- Interferon antagonism (NS-1)
- „Gene constellation“

Only „vague“ molecular predictors available!

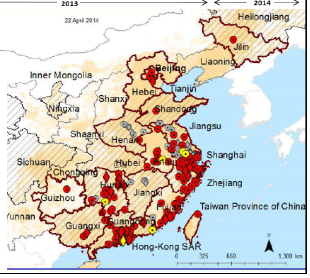




H7N9/China

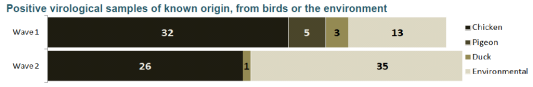


- Mainly elderly affected
- 427/147 cases (22.4.14)
- 2 waves of infections; cases continue to be reported
- Contact to infected poultry at live bird markets

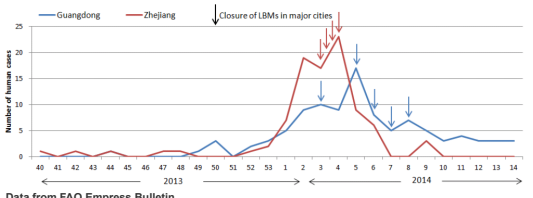


H7N9, … where exactly are the avian reservoirs?

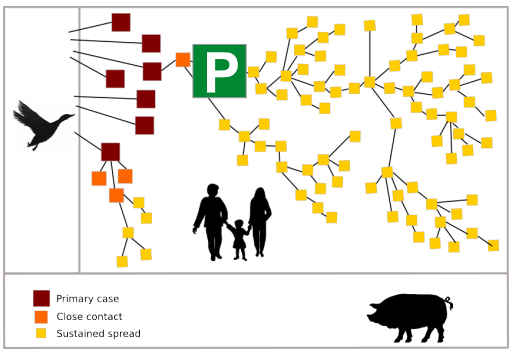
Positive virological samples of known origin, from birds or the environment



Sample origin could not be determined for 64 additional samples (35 in wave 1, 29 in wave 2); 74 additional positive virological samples (9 chickens, 1 tree sparrow, 64 environmental) were reported in peer-reviewed articles (1, 2, 3, 4, 5, 7).



Data from FAO Empress Bulletin



What renders animal influenza viruses pandemic?

- Transmissibility (aerosol-driven)
- Replication efficacy in the upper respiratory tract
- Immune escape (human population as „virgin soil“)

Less than vague molecular predictors available:
Humans as sentinels…

Increasing threats at animal-human interfaces

- Expansion of global travel and trade
- Increasing sizes and densities of human and poultry populations
- Expansion of agricultural land use
- Encroachment of wildlife habitats
- Changing human behaviour
  (e.g., demands for free-range poultry rearing)

Prevention and intervention

- Preventing pathogen exposure:
  - Improved, tailored biosecurity
  - Safer trading (LBMs)
- Monitoring for AI (wild birds and poultry)
  - Risk-based surveillance programs
  - Rapid and specific diagnostics
- Appropriate restriction measures
- Vaccination as a last resort

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Professor Paul Barrow
University of Nottingham

Food safety threats

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Food Safety Threats

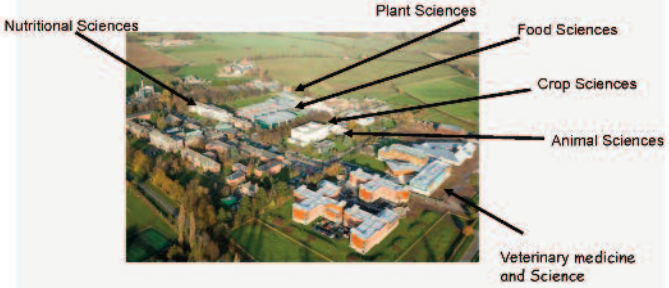
P. A. Barrow
School of Veterinary Medicine and Science
University of Nottingham, UK

Global Top 100 University

Sutton Bonington Campus

The University of Nottingham

A major UK centre for Agri-Vet-Food Sci research



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1. Major population, environmental, trade and production factors affecting disease and food safety
2. Salmonella,
3. Campylobacter
4. Clostridium difficile
5. E. coli
6. Control – options

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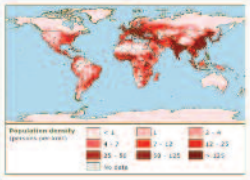
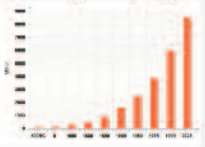
A common challenge for mankind

The University of Nottingham

Population pressure ....
High ....



and getting higher



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A common challenge for mankind

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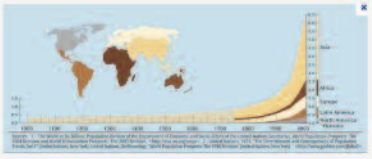
Increasing population is occurring disproportionately in the developing countries and has a number of effects in terms of agriculture and food production.



This has a number of consequences of relevance for global food safety

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Increased living standards = increased meat consumption

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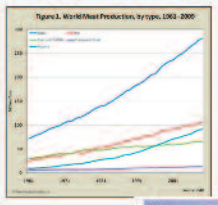
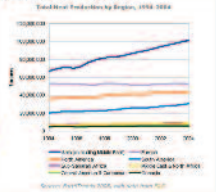
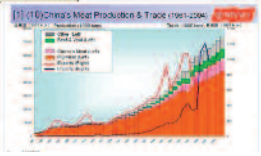
Increases in living standards in many countries are followed by increased demand for a meat-rich diet



Since 2000 global meat production has risen by in excess of 20%
Demand has doubled in the last 30 years



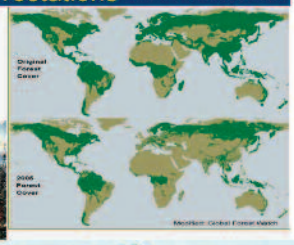
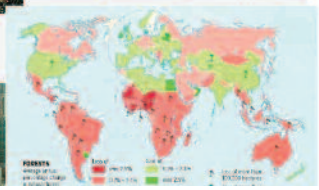


= increased demand for space for farm = increased deforestations

Increasing population means **increased demand for space** – for habitation and food production including livestock rearing. This leads inevitably to encroachment on virgin land with **deforestation**.

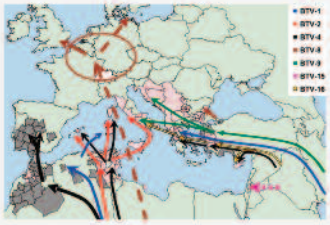




These lead to climate change as an additional factor

Bluetongue in sheep, goats and cattle – spread of serotype 8 into northern Europe.



Could we see an increase in open-sided poultry housing in previously temperate countries??

Increased travel and global trade

International trade and vector spreading – *Aedes albopictus* – transmits West Nile, yellow fever, dengue and Chikungunya – international goods and human travel – associated with humans not wetlands


2007 Native range

Variations in production methods

Variations in hygiene exist with huge variation in health status

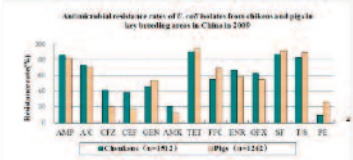


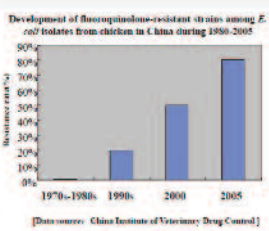

Variations in production methods

Distribution of production. In some countries production by large companies is "delegated" to small farms – again with potential animal health and welfare issues



Insufficient regulation of antibiotic use





[Data sources: China Institute of Veterinary Drug Control]

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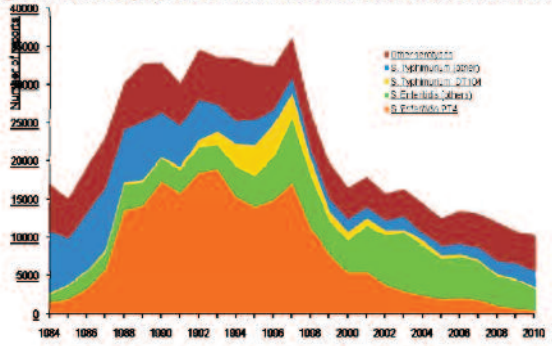
Salmonella – surely not a new problem?

The University of Nottingham

Figure 7: Laboratory reports of human *Salmonella* cases in the UK, 1984-2010



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Most prevalent serovars *S.* Enteritidis, *S.* Infantis and *S.* Typhimurium

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Appearance of monophasic *S.* Typhimurium

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S. Typhimurium is 4,[5],12:i:1,2

In 1990s a strain in Spain 4,[5],12:i;- which was phage type U302 no *fljB* gene by PCR (phase 2 flagellin)

Since 2006 *fljB* PCR- strain which was DT193 appeared in Germany – also other EU countries.

Genetic characteristics indicate that they are derivatives of the circulating strain – rather than a new serotype

- S. Enteritidis O1,9,12: H gm:-
- S. Typhimurium O1,4,[5],12:H i:1,2
- S. Typhimurium O4,[5],12:i;-

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Mono- aphasic group D *Salmonella* serovars

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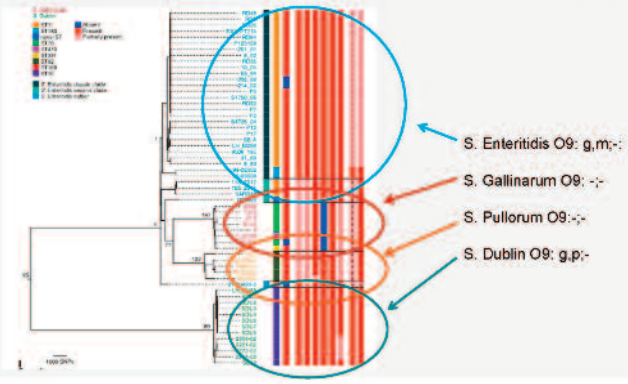

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Mono- to aphasic group *Salmonella* serovars – an evolutionary process?

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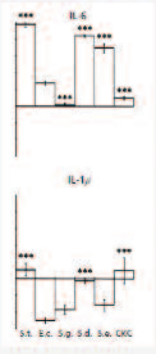
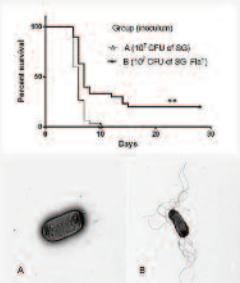
S. Gallinarum is non-flagellate and is less inflammatory than other serovars



S. Gallinarum manipulated to be flagellate is more inflammatory, and less virulent than the non-flagellate parent strain



Is the monophasic S. Typhimurium evolving in the same direction?

Global Top 100 University

Campylobacter

The University of Nottingham

Campylobacter - current and future issues of major importance/interest?

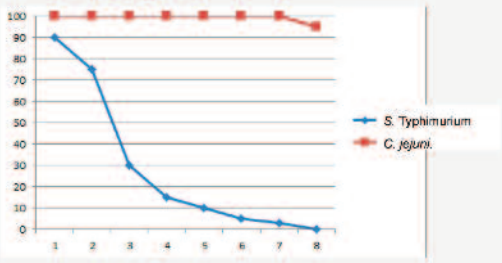
Involvement of other spp. *C. coli*, *C. lari*, in wider world.

Multiple antibiotic resistance in *C. jejuni* and *C. coli* (aminoglycosides, macrolides) in China and other countries

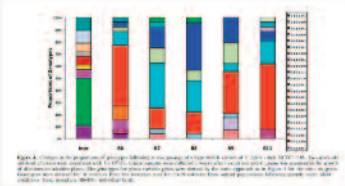
Work on vaccines and [illegible]

C. jejuni has ability to avoid immune control

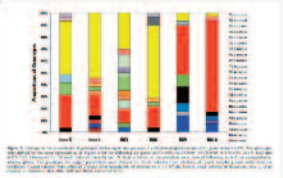
Campylobacter – absence of clearence



Campylobacter – absence of clearence



Homopolymeric tracts (sequences of 9-10 identical bases – errors in replication)



11-29 Genes switch off and on – surface genes.

Can we fix these in one position to generate a realistic live vaccine?

Bayliss et al., 2012
NAR

Campylobacter

Campylobacter - current and future issues of major importance/interest?

Involvement of other spp. *C. coli*, *C. lari*, in wider world

Vaccine-based control??
Economics?
Can it work??
Work of Wyszynska et al (2004) CjaA-based vaccine (N-glycosylated lipoprotein) – very variable protection, also Peb1A)

The other potential major players:

E. coli – EHEC (O157:H7) in poultry? Parallel *S.* Choleraesuis??

Clostridium – *C. difficile* in poultry (1-18% in boilers) – new zoonotic agent?, *C. perfringens*

Pathogenic *E. coli* - EHEC

The other potential major players:

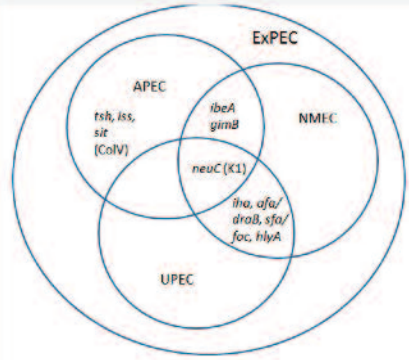
E. coli – EHEC (O157:H7) in poultry?

Rarely in chickens – more in turkeys (3.6% cattle, 7.5% turkeys, 0.9% chickens)
Isolation of Stx –ve strains

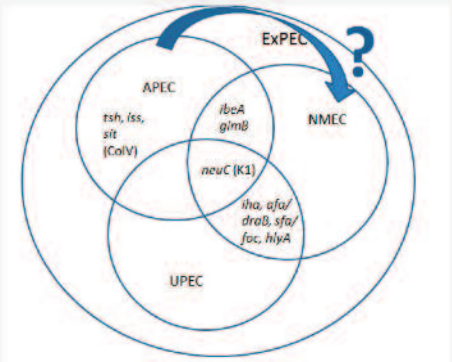
Anomaly of colonising ability <10 months!!

Parallel *S.* Choleraesuis??

Pathogenic *E. coli* - APEC



Pathogenic *E. coli* - APEC



Clostridium perfringens

The other potential major players:

Clostridium – C. difficile in poultry (1-18% in boilers) – new zoonotic agent?, *C. perfringens*

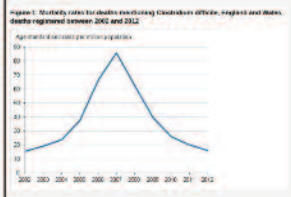
Growth promoting antibiotic use α necrotic enteritis

CDC 2013 (C. perfringens 5% of all fp disease)
Outbreaks of fb disease 3452 cases *C. perfringens*/poultry
2963 *C. perfringens*/cattle

The rest of the world??

Clostridium difficile ??

Major cause of morbidity in hospitals – now controlled?



Withdrawal of growth promoters – an effect?

Texas (2011)
2.3% broilers positive
Meat 1-12% (all Tox –ve)

Canada (2010)
12% chicken carcasses positive – ribotype 078 (human type)

Austria (2009)
3.4% broiler chickens Tox A + B

The power of ideas

Francis Bacon

Philosopher and English scientist (1561-1626)

Essay on Innovations.

"He that will not apply new remedies must accept new evils".

WVPA Europe Meeting 2014

Paul McMullen
Poultry Health Services

Antibiotic resistance

Emerging Avian Health Threats: Antibiotic Resistance

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How have we got here?

Antibiotic- , or, more generally, antimicrobial- resistance has emerged as a 'hot topic' for the poultry industry over the past 15 years. It is one which generates much debate and often alarmist claims (at least with respect to human health), and an often-polarised debate. Personally, I rather doubt that even complete loss of antimicrobials through widespread resistance (if it were to occur) is likely to become an early cause of the extinction of *H.sapiens* on earth. It could, however, have very profound effects on society in many ways, so it is not surprising that it is emotive. As poultry veterinarians and scientists, our challenge is to help poultry producers to understand the issues and implement effective controls for the benefit of both the poultry industry and society.

Bacteria-like organisms have been present on this planet for about 4 billion years, and for much of that time have been engaged in intensive interaction (including predation, competition, and cooperation) and antimicrobials are sometimes produced in the process. It is therefore entirely to be expected that resistance to various antimicrobials will occur in natural microbial populations without our intervention. When microbial populations are exposed to effective antimicrobials, selection for resistance is to be expected in the same was as with natural selection.

The roots of the current debate can be traced to more general concerns about the consequences of our industrial society as exemplified by Rachel Carson's book 'Silent Spring'. Sulphonamide resistance in food animal isolates of Salmonella isolates was the stimulus for the Swan report which, among other recommendations, encouraged the separation of production-enhancing and therapeutic use of antimicrobials. Products used for production enhancement were to be from antimicrobial groups not perceived to be of high value for treatment of either animals or humans. This principle was subsequently incorporated into EU Directive 70/524 but not so widely followed outside Europe. By the 1990's some of the antimicrobial groups previously considered of little interest for medical treatment were being used again medically. This led to pressure to prohibit the use of all production-enhancing use of antimicrobials in Europe, and this came to fruition in 2005.

What are the issues?

Antimicrobial resistance can be an issue for both poultry health and human health.

Poultry medicine has made very significant advances over the last 100 years. These have included achieving a thorough understanding of immunosuppressive diseases, the control of which, through the use of hygiene and vaccination, helps ensure that the immune system is capable of dealing with a broad range of infectious diseases. Many other diseases are also controlled through biosecurity, vaccination and even eradication of some significant pathogens. Nevertheless primary bacterial infection sometimes requires medication, as can secondary infections with commensals such as *E.coli*, *Enterococcus*

ssp and *Staphylococcus ssp*. where these infections are epidemiologically and practically significant. For this reason, maintaining the efficacy of available approved treatments in poultry is important.

Various tools are deployed in support of this:

- Isolation and sensitivity testing of the target pathogen
- Good feed and water hygiene
- Avoiding prolonged or repeated treatments as far as possible
- Replacement of a healthy normal flora post treatment – typically by the use of products introduced in the 1990's for competitive exclusion of Salmonella sp.

In spite of all of the progress made, there continue to be many challenges:

- High feed costs associated with diversion of grain into energy production
- Increasing restrictions on biocide use and loss of medicines licenses
- High biosecurity systems delaying infections to an age in which they have a greater impact and, perhaps increasing the variability of immune status between flocks.

It is the public health threats which most concern society. There are, essentially, 3 routes by which animal use of antimicrobials can affect public health:

- Increased prevalence of resistance genes in zoonotic bacterial pathogens with transfer directly (to farm visitors, farm staff, veterinarians) or, through inadequate food hygiene, to susceptible humans.
- Increased prevalence of resistance genes in commensal bacteria, again with either direct or indirect transfer, via food, to humans, and subsequent transfer of these genes into pathogens.
- Contamination of the environment with residues of antimicrobials through disposal of carcases, or litter, such that pathogens or commensals are exposed to selection and reach the human population directly or indirectly through pets and farm animals.

In human medicine itself there is a raft of important associated issues such as hospital acquired infections, immunosuppressive diseases, clinical management involving deliberate immunosuppression, treatments disturbing intestinal flora with resultant *Clostridium difficile* overgrowth and so on. Arguably the great majority of antimicrobial resistance issues (*Klebsiella pneumonia*, tuberculosis, malaria, venereal disease) are unrelated to any animal use of antimicrobials. The two issues which are currently being linked to agricultural systems are livestock-associated methicillin resistant *Staphylococcus aureus* (LA_MRSA) and extended-spectrum beta-lactamase resistance, mainly of *E.coli*.

Whereas in the 1960's attention was directed at sulphonamide and chloramphenicol resistance, today the main focus is on cephalosporins and flouroquinolones as these are groups of actives considered to be of critical importance in human medicine. Currently we have an interesting contrast in how these issues are approached in regulation of poultry medicines the USA and the European Union. In the USA flouroquinolones are

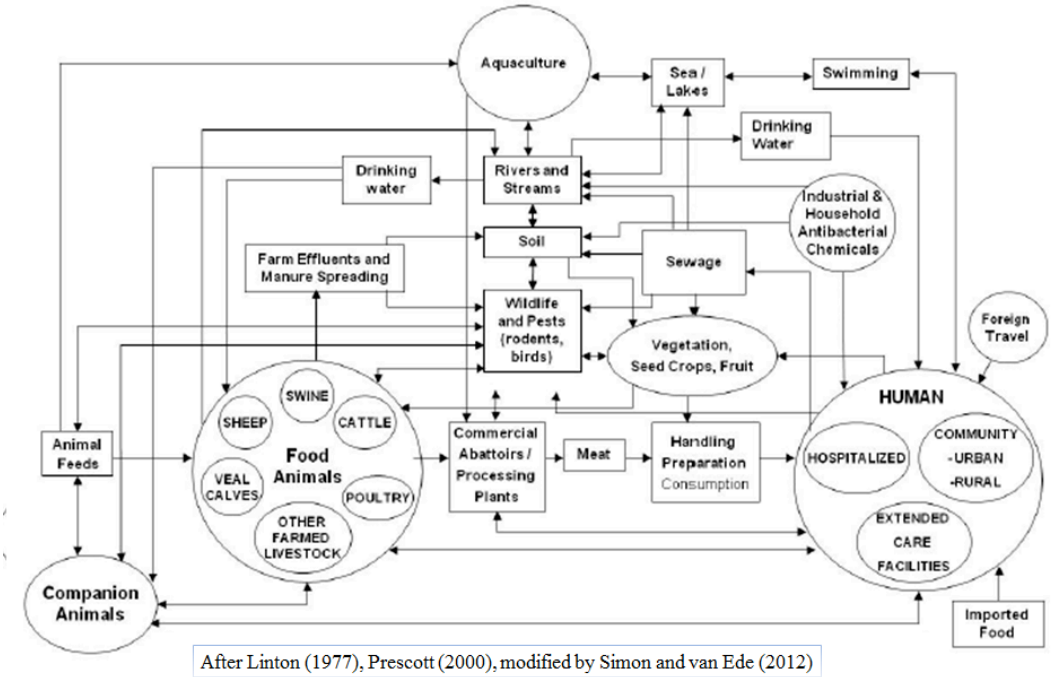
prohibited, and cephalosporins licensed for day old use (but prohibited off label, whereas in the EU cephalosporins are not licensed (and prohibited in off-label use), and flouroquinolones are approved for use.

Why does transmission occur?

The epidemiology of antimicrobial resistance is, it is generally agreed, complex. Studies carried out in this area often use varied methods for the selection of the organisms to be assessed, and even different 'break points' for determining that isolates are resistant. Use of selective broths and plating out media have the potential to identify tiny proportions of a population with reduced sensitivity or a high degree resistance but these may or may not be epidemiologically relevant, either for the poultry or for public health.

Figure 1 below (from Simon & Van Ede 2012) illustrates the complexity of this topic. Many of the paths show two-headed arrows, suggesting that transmission can potentially occur in either direction. For all it's complexity this diagramme remains incomplete. There is, for example no reference to imported livestock or feed ingredients, nor does it show the link between aquaculture and food handling.

Figure 1 Epidemiology of Antimicrobial Resistance



After Linton (1977), Prescott (2000), modified by Simon and van Ede (2012)

A recent review of veterinary use of antimicrobials over the past 60 years (Guardabassi,2013) nicely summarised the current situation as follows:

"*The contribution of veterinary antimicrobial use to resistance problems in human medicine has always been and probably always will be a controversial topic. This topic is*

subject to multiple opinions and divergence as it involves ethical issues on animal welfare and human health, as well as economic interests by the pharmaceutical industry, the food industry and various professional categories, including farmers, veterinarians, pharmacists and researchers. As a consequence of all these factors, the debate on antimicrobial use in animals is often vigorous and not always scientifically unbiased. My personal opinion, based on 17 years of research in this area, is that the vast majority of the resistance problems observed in human medicine, especially the most critical ones associated with multidrug-resistant bacteria in nosocomial infections, including MRSA and ESBL-producers, are largely attributable to human antimicrobial use. However, even relatively small numbers may be important in this context since the level of acceptable risk is likely close to zero when human life is put at risk by the use of antimicrobials in animals."

Where are we going?

It seems unlikely that this debate is either going to go away, nor, on the other hand, will it re-write the basic rules of economics. Attempts to solve the problem by prohibitions and bans, where use is economically justified, are unlikely to be successful unless associated with trade restrictions on countries which do not impose or enforce the same prohibitions. Reduction in the need to use antimicrobials, as well as in the inappropriate and uneconomic use, might be more effectively achieved by research and education.

It would also be a mistake to think that economic pressures only apply in agriculture. Highly effective systems for the control of MRSA in hospital environments have relied, in part, on testing incoming patients for carriage of resistant pathogens and increased isolation for those which are positive. But both the testing and isolation costs money, so we can expect an increased focus from medical colleagues in understanding the source and epidemiology of such infections with a view to limiting these costs. A recent paper has estimated the increase in human life expectancy attributable to antibiotics might be 2 to 10 years, and that this is worth US$60 to 300 trillion to the US economy (valued at US$100k per life year). However these authors argue against bans and prohibitions but in favour of fees and taxes on antimicrobial use to distribute the economic cost of antibiotic use more widely. The key to any such proposals would lie in the detail of its implementation and the major challenge of avoiding unintended consequences.

As poultry veterinarians we can directly influence only a small part of the complex system illustrated in Figure 1, but it remains important to play our part fully and well. Colleagues are actively engaged in helping develop and implement rational guidelines to help ensure the responsible use guidelines such as the recently launched Responsible Use of Medicines in Agriculture Alliance (RUMA) Guidelines, which were updated with the active support of the BVPA.

There are a range of regulatory initiatives ongoing relevant to this topic. For instance the European Commission has asked the European Medicines Agency for advice on the impact on public and animal health of the use of antibiotics in animals – the request has been consulted on and the target for reporting is June 2014. Harmonised monitoring of

AMR across EU member states is targeted to begin from January 2014 (under the Zoonoses Directive 2003/99) and AMR is likely to figure in the new Animal Health Law currently being formulated.

I believe that poultry veterinarians are well placed to participate in rational debate in this topic. We have been very active in implementing effective pathogen control programmes directed both at poultry pathogens and zoonoses and have direct responsibility for antimicrobial use because, at least in the EU, they are prescription medicines. It is in the long-term interest of the poultry industry that we both conserve efficacy of existing antimicrobials and contribute to the development of technologies which reduce the need for medication and the prevalence of resistance which poses significant risks to human health.

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Guardabassi,L. (2013) Sixty years of antimicrobial use in animals: what is next? Veterinary Record 2013;173:599-603

Hollis,A. and Z. Ahmed (2013) Preserving Antibiotics, Rationally N Engl J Med 369;2

Simon, A. J., and C. van den Eede. (2013) "Antimicrobial Resistance: An overview of the current issues and concerns." *CATTLE PRACTICE* 21 (2013): 67-77.