

Landmark papers on the consequences of antibiotic use in farm animals for humans

Pierre Tattevin

Infectious Diseases and ICU, Pontchaillou Univ. Hosp., Rennes, France

In 1976, almost 40 years before the emergence of the 'One Health' concept, Stuart Levy and colleagues published pioneering works on the connection between increased use of antimicrobials in farm animals, and the emergence of antibacterial resistance in humans^{1,2}

The first landmark paper was published in the prestigious *Journal Nature* in March 1976²: The authors transferred a mutant plasmid *pSL222-6* expressing resistance to chloramphenicol, tetracycline, sulphonamides and streptomycin into *Escherichia coli*, and introduced them directly into the intestines of four chickens. Then, chickens were fed with tetracycline-supplemented food, to enhance colonisation with tetracycline-resistant *E. coli*. The authors could verify that all chickens were indeed colonised. Two chickens each were then placed in two cages (A and C), each containing 50 chickens. One cage (A) was placed on tetracycline-supplemented feed, the other (C) was not. Two other cages of 50 chickens with (B), and without (D) tetracycline-supplemented feed, were placed approximately 50 feet from the experimental cages.

Table 1 Number of chickens excreting *E. coli* containing *pSL222-6**

Day	Cage			
	A	B	C	D
0	0	0	0	0
7	1	4	0	0
14	1	6	0	0
49	5	8	0	0
56	6	8	0	0
63	7	12	0	0
% Chickens excreting mutant R plasmid	14	24	0	0

* Does not include inoculated chickens placed in cages A and C: chickens in cages A and B were fed tet-feed; C and D received normal feed.

Stuart Levy and colleagues could demonstrate (Table):

- i) the spread of tetracycline resistance among chickens in the cage where food was supplemented by tetracycline (A), but not in the other cage (C), a demonstrative illustration of the selective pressure;
- ii) transmission of resistance even in a distant cage, if chickens receive tetracycline-supplemented food (cage B), but not in the absence of this selective pressure (cage D).

During these experiments, they also screened the faeces from 11 family members living on the farm, and three laboratory workers, for the presence of the plasmid. On two occasions, the plasmid was detected but only temporarily. The absence of antibiotic use in these two humans probably explains why the plasmid was only temporarily detected. The authors could not determine if the transmission of tetracycline resistance

between two distant cages (50 feet) occurred by air or on the clothes of the feed handler².

That same year, a few months later (September 1976), Stuart Levy published in the *New England Journal of Medicine* a clear demonstration that antibiotic-supplemented feed is a factor contributing to the selection of antibiotic-resistant bacteria in humans¹. They showed, at a larger scale, that:

- i) intestinal flora of chickens fed with tetracycline-supplemented food contained almost entirely tetracycline-resistant organisms, and that this emergence occurred early (within one week after tetracycline-supplemented food was started);
- ii) the farm workers became progressively colonised by tetracycline-resistant organisms, although much more slowly, and at lower rates: within six months, 31.3% of weekly faecal samples from farm dwellers contained >80% tetracycline-resistant bacteria in farms where chickens were fed by tetracycline-supplemented food, as compared to 6.8% of samples from the neighbours' farmers who fed their chickens with antibiotic-free food (P<0.01)²

The concluding sentence was prophetic:

"These data speak strongly against the unqualified and unlimited use of drug feeds in animals husbandry and speak for re-evaluation of this form of widespread treatment of animals."

Unfortunately, it took several decades before the world realised how true, and how important, these pioneering works were!

References

1. Levy SB *et al.* Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. *N Engl J Med.* 1976;295:583-8
2. Levy SB *et al.* Spread of antibiotic-resistant plasmids from chicken to chicken and from chicken to man. *Nature.* 1976;260:40-2