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Original Research Paper

PORCINE RESPIRATORY DISEASE COMPLEX (PRDC) - A META-ANALYSIS AND SYSTEMATIC REVIEW OF THE EFFICACY OF ENROFLOXACIN

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Summary: Porcine respiratory disease complex (PRDC) is an economically significant disorder characterised by slow growth, decreased feed efficiency, lethargy, anorexia, fever, cough and dyspnea. A meta-analysis is a method of surveying and combining results of several independent clinical trials. Systematic reviews are concise summaries of the best available evidence that address sharply defined questions; they seek to assemble and examine all the high quality evidence on any given subject. This includes a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles for review. Enrofloxacin is a fluoroquinolone chemotherapeutic that was developed exclusively for use in veterinary medicine. The overall result of meta-analysis indicates a high efficacy of enrofloxacin ($P < 0.001$) in treating PRDC. The mortality rate was lower in the groups which used enrofloxacin ($P = 0.037$). Low resistance of all bacteria that cause respiratory tract infections was characterized from 0 to 7,6 %. The high efficacy of enrofloxacin in PRDC and its beneficial economic effect has been confirmed by meta-analysis and systematic review.

Key words: fluoroquinolones; meta-analysis; pigs; porcine respiratory disease complex

Introduction

The aim of the study is examining the effectivness of enrofloxacin in treatment of PRDC. Efficacy of treatment, influence on mortality and susceptibility of pathogens were the main criteria for assessment.

Porcine respiratory disease complex (PRDC) is a multi-factorial respiratory syndrome and is economically significant for pork producers throughout the world. PRDC is characterised clinically by slow growth, decreased feed efficiency, lethargy, anorexia, fever, cough and dyspnea and is common in pigs around 10 to 20 weeks of age. Because PRDC is not caused by a single organism the pathogens isolated from pigs vary between and within production units (1).

Most commonly porcine reproductive and respiratory syndrome virus (PRRSV), swine influenza virus (SIV), porcine circovirus type 2 (PCV2), pseudorabies virus (PRV), *Mycoplasma hyopneumoniae, Bordetella bronchiseptica, Actinobacillus pleuropneumoniae, Pasteurella multocida, Streptococcus suis* and *Haemophilus parasuis* are evidenced in PRDC incidences (2). Beside pathogens also environmental factors, new technologies (early weaning, multisite and age segregated systems), tendency to increase the size of finishing units and their numbers of sourcing farms, lower weaning age are contributors for PRDC (3).

A number of tests can be used to determine when these infections are occurring: post-mortem examination with organism identification, serological profiling, polymerase chain reaction (PCR) (4).

Control of PRDC is first based on the proper management of production imports such as the environment, nutrition, biosecurity and husbandry procedures (4).

In addition is recommended other management strategies that help to limit the impact of MH what include a balanced and stable sow herd with fewer than 30% replacement gilts, closing the herd or minimizing the number of sources to procure pigs, mul-

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tisite production, biosecurity to prevent the spread and introduction of disease, reduction of stress on pigs, optimal stocking density, and adequate ventilation, air quality and room temperature (5).

Antibiotic therapy is often used to control PRDC. Feed, water and injectable medications are available. Treatment programs to eliminate infection within a group of pigs or pulse medication are procedures that is reducing clinical disease (4).

The successful use of combination therapies with antibiotics has also been reported (6).

Vaccination is a common control method for PRDC control (4). The economic benefit of MH vaccination has been demonstrated (7).

Vaccination programs for PCV 2, PRRS, SIV and PRV are implemented in countries where vaccines are available.

Once we understood what is circulating, then control programs can be in place (vaccination, medication) to try to avoid clinical outbreak.

A meta-analysis is a method of surveying and combining results of several independent clinical trials. The term meta-analysis was first used by Glass in 1976, who, with his associate Mary Lee Smith, statistically compiled the results of 375 studies dealing with the efficacy of psychotherapy.

The most frequently used definition is the one by Huque: meta-analysis refers to a statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable (8). Besides quantitative integration, a meta-analysis vastly improves the potential for uncovering and studying any differences in the available scientific material and provides a basis for plausible explanations of them. It can also lead to new discoveries.

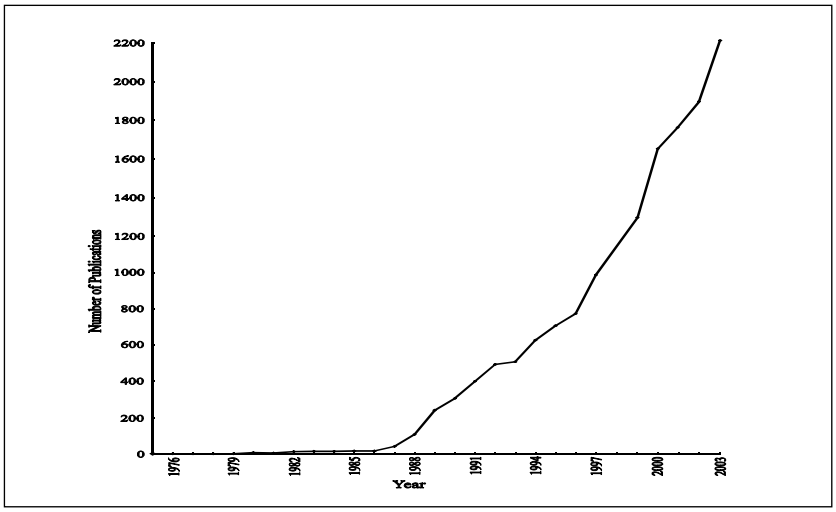
A brief summary of the procedures involved in a meta-analysis would comprise the following logical steps:

1. the definition of the problem and the inclusion criteria for the studies;
2. positioning, classifying and coding the characteristics of individual studies and the quantitative measurement of their characteristics;
3. the integration of the results and a comparison with the characteristics of the studies (analysis and explication of results); and
4. reporting of the results (9).

Systematic reviews are concise summaries of the best available evidence that address sharply defined questions; they seek to assemble and examine all the high quality evidence on any given subject. This includes a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles for review. When the results of primary studies are summarized but not statistically combined, the review may be called a qualitative systematic review. A quantitative systematic review, or meta-analysis, is a systematic review that uses statistical methods to combine the results of two or more studies (10).

This analytical method is of particular importance in the assessment of therapeutic efficacy when individual studies do not provide an overview over all studies on a topic. As their samples are too small, individual studies cannot provide a quantitative evaluation of the effect of treatment, nor can they test null hypothesis. Prior to meta-analysis, the traditional method was a narrative discourse on previous findings, which, however, could be misleading and subjective.

In the past few years, meta-analysis has been increasingly used in all fields of science. This is particularly evident for the medical science, as shown in graph 1.



Graph 1: Number of publications 1975-2003 that used meta-analysis (modificated after Petitti (11))

Investigating the efficacy of certain drugs can be done in several ways: by *in vitro* susceptibility profiling of certain bacteria, by clinical trials or by using meta-analyses or systematic reviews.

Enrofloxacin is a fluoroquinolone chemotherapeutic that was developed exclusively for use in veterinary medicine. Shortly after its administration, extremely low concentrations have a bactericidal effect against most Gram-negative and Gram-positive bacteria and will also act against mycoplasmata. It acts against both bacteria in the multiplication phase and dormant microorganisms. It is effective in the presence of oxygen and, owing to this phenomenon, it does not damage beneficial anaerobic intestinal microflora.

The efficacy of fluoroquinolones is related to both the maximum concentration and the time above their MIC value. *In vitro* pharmacokinetic models have shown that maximum concentrations of active substances, 8 times in excess of their MIC, have been able to reduce the number of bacteria by up to 99 % and inhibit their growth for up to 24 hours. The intensity of exposure may be quantified as the ratio between the area under the time-concentration curve (AUC) and the minimum inhibitory concentrations for the causative pathogens (MIC); a short term for this ratio is AIUC – area under the inhibitory plasma concentration curve. For example, if in an enrofloxacin therapy the AIUC is higher than 125, the probability of a clinical and microbiological cure is above 80 %, otherwise it is only 42 % or 26 % in respect of a microbiological cure. Resistance to fluoroquinolones is also reduced to a minimum if these parameters are taken into consideration – C_{max}/MIC ratio is at least 8-10 and AUC/MIC at least 100-125 (12, 13).

Material and methods

Table 1: Short survey of studies included in meta-analysis and systematic review

Author, year of publication, number of animals included	**Meta-analysis and systematic review parameters**
	Comparative control group
1. Altrock 1998 (14)	- lesions - incidence of bacteria - *in vitro* susceptibility testing of *P. multocida, B. bronchiseptica, A. pleuropneumoniae, H. parasuis, B-haemolytical streptococci*
	- 23 antimicrobial agents (*in vitro* susceptibility)
2. Köfer et al. 1992 (15)	- lesions - incidence of bacteria - *in vitro susceptibility* testing of *P. multocida, B. bronchiseptica, A. pleuropneumoniae, H. parasuis, P. haemolytica, Streptococcus* spp.
	- 8 antimicrobial agents (*in vitro* susceptibility)
3. Rose et al. 1996 (16); n = 551	- clinical efficacy - mortality
	- comparative control group (cefquinome, amoxicillin)
4. Kobish et al. 1990 (17); n = 69	- clinical efficacy - mortality
	- negative control group - positive control group
5. Awad-Masalmeh and Schuh 1990 (18); n = 129	- clinical efficacy - *in vitro* susceptibility testing of *P. multocida, B. bronchiseptica, A. pleuropneumoniae, M. hyopnemoniae* - economic parameters
	- autogenous vaccines - 4 antimicrobial agents (*in vitro* susceptibility)

6. Ganter et al. 1995 (19); n = 64	- *in vitro* susceptibility testing of *P. multocida, B. bronchiseptica, A. pleuropneumoniae, H. parasuis*, S. suis 2
	- 10 antimicrobial agents (*in vitro* susceptibility)
7. Pommier et al. 1998 (20); n = 326	- clinical efficacy - economic parameters
	- comparative control group (spiramycin)
8. Flaßhoff 1996 (21); n = 40	- susceptibility testing of α-hemolytic streptococci, *P. multocida, B. bronchiseptica*
	- 8 antimicrobial agents
9. Wu et al. 1997 (22)	- *in vitro* susceptibility testing of *Mycoplasma hyopneuminiae* and *M. hyosynoviae*
	- 11 antimicrobial agents
10. Hannan et al. 1997 (23)	- *in vitro* susceptibility testing of *Mycoplasma hyopneuminiae*
	- 2 antimicrobial agents
11. Kobayashi 1996 (24); n = 92	- *in vitro* susceptibility testing of *Mycoplasma hyosynoviae* and *M. hyorhinis*
	12 antimicrobial agents
12. Herrerias et al. 1995 (25); n = 150	- clinical efficacy
	- control groups (norfloxacin, trimetoprim-sulfametoksazol)
13. Asawa et al. 1995 (26)	- *in vitro* susceptibility testing of *A. pleuropneumoniae*
	19 antimicrobial agents
14. Dom et al. 1994 (27)	- *in vitro* susceptibility testing of *A. pleuropneumoniae*
	9 antimicrobial agents
15. Yeh and Park 1996 (28)	- *in vitro* susceptibility testing of *A. pleuropneumoniae*
16. Salmon et al. 1995 (29)	- *in vitro* susceptibility testing of *A. Pleuropneumoniae, P. multocida, S. typhimurium, S. cholerae-suis, E. coli*, S. suis, β- hemolytic streptococci
	- 8 antimicrobial agents
17. Hornedo et al. 1988 (30); n = 6	- clinical efficacy
	- negative control (untreated animal)
18. Gutierrez et al. 1993 (31)	- *in vitro* susceptibility testing of *A. pleuropneumoniae*
	- 41 antimicrobial agents
19. Wallgren et al. 1998 (32); n = 64 Parenteral aplication	- clinical efficacy - lesions - re-isolation of *A. pleuropneumoniae* - economic parameters
	- control (uninfected animals, infected untreated animals) - treatment (penicillin, danofloxacin, ceftiofur, tiamulin)
20. Wallgren et al. 1998 (33); n = 112 Peroral aplication	- clinical efficacy - lesions - re-isolation of *A. pleuropneumoniae* - economic parameters
	- control (uninfected animals, infected untreated animals) - treatment (, penicillin, chlortetracycline, florfenicol, tilmicosin, tiamulin)

21. Pijpers et al. 1998 (34); n = 21	- clinical efficacy - lesions - re-isolation of *A. pleuropneumoniae* - economic parameters
	- inoculation with *A. pleuropneumoniae* - negative control (untreated animal) - treatment (oxytetracycline)
22. Chung and Yeh 1993 (35); n = 25	- lesions - economic parameters
	- negative control - treatment (ceftiofur, oxytetracycline)
23. Gutierrez Martin and Rodriguez Ferri 1993 (36)	- *in vitro* susceptibility testing of *Pasteurella multocida* subspecies *multocida*
	- 41 antimicrobial agents
24. Ikoma et al. 1994 (37); n = 155	- clinical signs
	- comparative treatment (danofloxacin)
25. Heinen et al. 1998 (38); n = 8	- pharmacokinetic study and *in vitro* susceptibility (*P. multocida, A. pleuropneumoniae, M. hyopneumoniae*)
26. Stipkovits et al. 1994 (39)	- *in vitro* susceptibility testing of 7 bacteria
	- 3 combinations of antimicrobial agents
27. Kołodziejczyk et al. 1999 (40); n = 2065	- clinical efficency
	- *in vitro* susceptibility testing of 7 bacteria - negative control groups
28. Ganter and Amtsberg 1996 (41)	- *in vitro* susceptibility testing of *Pasteurella multocida* and *Streptoccocus suis*
	- 10 antimicrobial agents
29. Silva et al. 1999 (42); n = 84	- *in vitro* susceptibility testing of *P. multocida, A. pleuropneumoniae, B. bronchiseptica*
	- 7 antimicrobial agents
30. Smith et al. 1991 (43); n = 64	- clinical efficacy - lesions
	- infected control groups - uninfected control groups
31. Madsen and Larsen 1996 (44); n = 350	- treatment (attempt to eradicate pleuropneumonia and enzootic pneumonia) - treatment - control after treatment
32. Larsen et al. 1998 (45); n = 135	- treatment (attempt to eradicate pleuropneumonia and enzootic pneumonia) - lesions - clinical efficacy
	- vaccination against *A. pleuropneumoniae* - disinfection
33. Hofmo and Luim 1998 (46); n = 51	- treatment (attempt to eradicate pleuropneumonia and enzootic pneumonia) - serology
	- 2 antimicrobial agents (tiamulin, benzilpenicillin) - vaccination

34. Bada et al. 1995 (47)	- *in vitro* susceptibility testing of *A. pleuropneumoniae* - 10 antimicrobial agents
35. Habrun et al. 1997 (48)	- *in vitro* susceptibility testing of *A. pleuropneumoniae, P. multocida*
36. Friis and Szancer 1994 (49)	- *in vitro* susceptibility testing of *M. hyopneumoniae* and *M. hyosynovie* - 4 antimicrobial agents
37. Molnar 1992 (50)	- *in vitro* susceptibility testing of *A. pleuropneumoniae*
38. Scheer at al. 1996 (51)	- *in vitro* susceptibility testing of *A. pleuropneumoniae, P. multocida* - 8 antimicrobial agents
39. Flores et al. 1998 (52)	- *in vitro* susceptibility testing of *A. pleuropneumoniae* - 6 antimicrobial agents
40. Stephano et al. 1988 (53); n = 20	- treatment - clinical efficacy - positive control group - negative control group
41. Aarestrup et al. 2000 (54)	- *in vitro* susceptibility testing of *A. pleuropneumoniae*
42. Simon et al. 1990 (55); n = 60	- clinical efficacy - economic parameters - control group - tiamulin
43. Semjen et al. 1988 (56); n = 280	- clinical efficacy - economic parameters - 2 antimicrobial agents (tiamulin, tilozin)
44. Laak et al. 1991 (57)	- *in vitro* susceptibility testing of *M. hyopneumoniae, M. hyosynovie* and *M. flocculare* - 17 antimicrobial agents
45. Glaswisching et al. 1989 (58) n = 190	- clinical efficacy - untreated control group
46. Friis et al. 1994 (59)	- *in vitro* susceptibility testing of *M. hyopneumoniae* and *M. hyosynovie* - 4 antimicrobial agents
47. Chou et al. 1995 (60)	- *in vitro* susceptibility testing of *P. multocida* - 3 antimicrobial agents
48. Awad-Masalmeh et al. 1994 (61)	- *in vitro* susceptibility testing of *P. multocida* - 7 antimicrobial agents
49. Trolldenier 1996 (62)	- *in vitro* susceptibility testing of *P. multocida* and *M. haemolytica* - 14 antimicrobial agents
50. Bole-Hribovšek and Zdovc 2002 (63)	- *in vitro* susceptibility testing of *P. multocida*
51. Ikoma 1994 (64); n = 78	- clinical efficacy - lesions - control group - kanamicin

52. Udovičič et al. 1996 (65); n = 77	- treatment - clinical efficacy
	- vaccination
53. Werner-Tutschu et al. 1997 (66)	- *in vitro* susceptibility testing of *P. multocida* and *B. bronchiseptica*
	- 19 antimicrobial agents
54. Shin et al. 2004 (67)	- *in vitro* susceptibility testing of *A. pleuropneumoniae, P. multocida* and *B. bronchiseptica*
	- 8 antimicrobial agents
55. Aaerestrup and Jensen 1999 (68)	*In vitro* susceptibility testing of *A. pleuropneumoniae* (7 antimicrobial agents) – determination of MIC

It is evident from the table 1 that 55 studies were included in the survey (references from 14 – 67): 19 examined the usage of enrofloxacin in mixed respiratory infections, 14 studies of pleuropneumonia, 9 for enzootic pneumonia, 6 for pasteurellosis and 3 for atrophic rhinitis. There are 3 studies which dealt with pleuropneumonia and enzootic pneumonia.

Eleven clinical studies were included in two meta-analyses (efficacy and mortality), other studies provided a review of susceptibility status for PRDC pathogens to enrofloxacin and other comparable antibacterials. Mortality was reported in three studies only, however actual causes of deaths were not reported.

The total number of animals included in the meta-analysis (efficacy), was 3954, of which 1745 were from the enrofloxacin-treated groups of different studies and 2209 from their control or alternative treatment groups; and 668 (mortality), out of which 218 were from the enrofloxacin-treated groups and 450 from their control or alternative treatment groups.

A lot of studies examined the susceptibility profile of respiratory pathogens; all were comparative, except for two by Aaerestrup *et al.* (54). In total, there were 7866 strains of respiratory pathogens examined for their susceptibility to enrofloxacin. Some of the studies also dealt with the economic parameters and the pathoanatomical signs (e.g. lesions) in respiratory organs and their changes.

Evaluation method

The results of meta-analyses are presented graphically. The graphs show compiled data on authors of individual studies, the year of study publication or performance, a numerical comparison between the treated and the control group (shown as effect, expressed as odds ratios) and the mean values of effect size with 95% confidence intervals.

The odds ratio (OR) was used as a scale of magnitude for the effect size. Characteristic of OR is that a value of 1.0 means that a certain therapy has no effect; values below 1.0 indicate that the tested therapy (in our case the use of enrofloxacin) is better than that of the control or the comparator therapy group. Values above 1.0 indicate the advantage of the control or comparator therapy over the tested therapy. When in a graph the study presentation with its mean value and the two lines for the confidence interval does not intersect the value of 1.0, we speak about statistical significance at different levels, e.g. in 95-percent confidence intervals the P level of statistical significance equals 0.05; in 99-percent intervals it equals 0.01, etc.

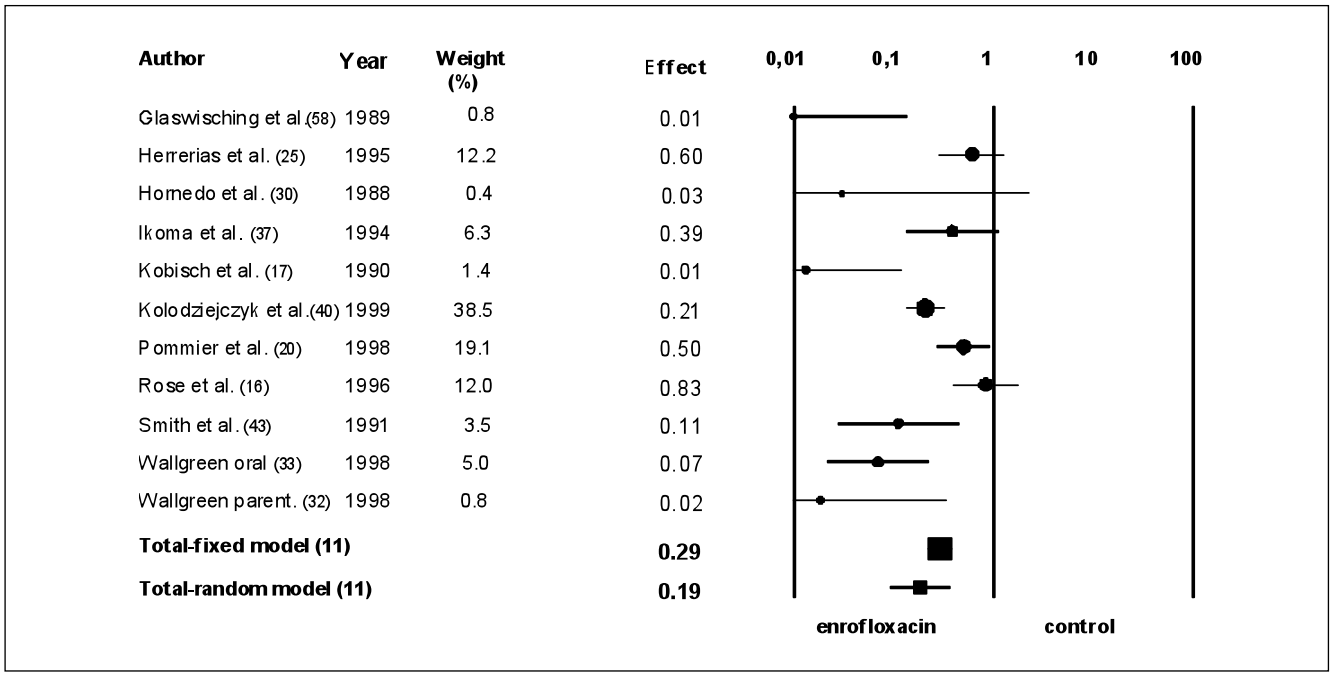
In cases, however, where mean values with confidence intervals intersect the 1.0 value line, we cannot speak about statistical significance.

The total effect size is always conditioned by weights of individual studies; therefore, in a meta-analysis we speak about a weighted total value of the effect size which, the same as for individual study is presented by mean value and confidence intervals. In the graph the weights for individual studies are shown as bigger or smaller full circles (●). This means that studies with smaller weights have smaller circles and those with larger weights have larger circles. The total effect size is shown as a full square (■). We also reviewed *in vitro* susceptibility of individual microbes to enrofloxacin as well to other antimicriobial substances and evaluated the MIC values.

The Comprehensive Meta-Analysis (69) computer programme was used for statistical analysis.

Results

Graf 2: Respiratory tract infections - efficacy of enrofloxacin treatment comparing with control group.

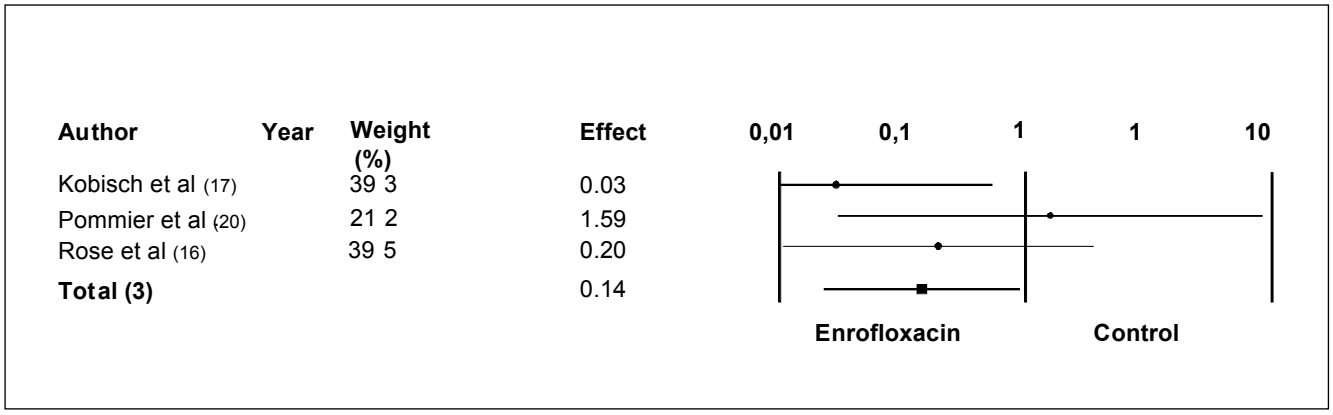


Homogeneity testing: Q = 43.1, d.f. (Q) = 10, P = 0.0003

Q.....heterogeneity value (χ^2 distribution);
d.f.....degrees of freedom ; P.... probability

It is evident from the graph that in the comparison of efficacy there is a statistically significant difference between the groups (P < 0.001).

Graph 3: Respiratory tract infections – comparison of mortality between enrofloxacin and control group. The mortality rate was lower in the groups which used enrofloxacin (P = 0.037) than in the comparative control groups



Homogeneity testing: Q = 2.62, d.f. (Q) = 2, P = 0.27

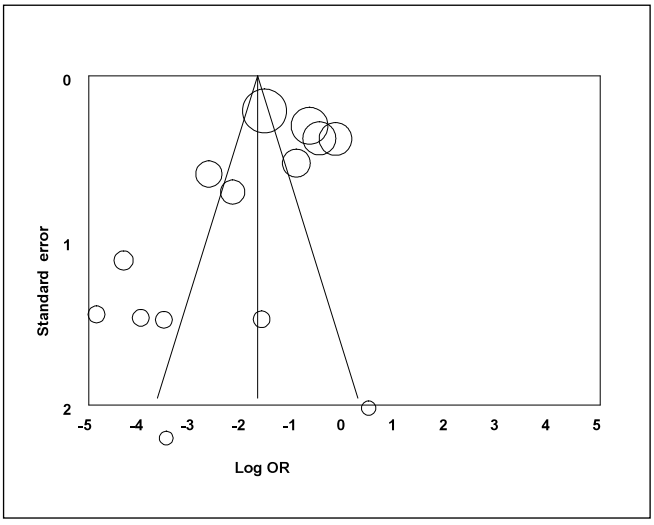
Table 2: In vitro susceptibility of respiratory pathogens to various antimicrobial substances (% of resistant strains) – summary of results from the reviewed articles

Antibacterial	*A. pleuropneumoniae*	*P. multocida*	*B. bronchiseptica*	*H. parasuis*
Gentamicin	6.4% (n = 235)	3.9% (n = 1142)	3.7% (n = 162)	9.5% (n = 42)
Trimethoprim/ sulfonamide	16.5% (n = 260)	19.9% (n =1141)	68.1% (n = 207)	30.9% (n = 42)
Enrofloxacin	2.3% (n = 2943)	2.8% (n = 2987)	7.6% (n = 904)	0.0% (n =124)
Kanamycin	3.3% (n = 87)	6.6% (n = 872)	7.0% (n = 106)	3.1% (n = 31)
Neomycin	10.3% (n = 223)	8.5% (n =1036)	3.4% (n = 148)	4.8% (n = 42)
Ampicillin	14.0% (n = 205)	15.1% (n = 1408)	57.7% (n =153)	23.3% (n = 30)

5.4% of all strains of *M. haemolytica* (n = 908) were resistant to enrofloxacin.

Table 3: Minimal inhibitory concentrations (MICs) for respiratory pathogens (enrofloxacin)

Bacteria	**MIC (µg/ml)**	**Bacteria**	**MIC (µg/ml)**
P. multocida	≤ 0.03-0.5	*M. haemolytica*	≤ 0,03-1.0
B. bronchiseptica	0.125-0.25	*A. pleuropneumoniae*	≤ 0,03-0.06



Graph 4: Funnel plot standard error by effect size (odds ratio – OR)

The funnel plot interprets dispersion of data. If heterogeneity is insignificant, data form a funnel with a wide opening of the funnel at the bottom of the graph and spire on the top. This way of presentation shows good agreement with the calculation of heterogeneity and funnel plot.

From funnel plot (graph 4.) it is evident that the studies included in the meta-analysis were heterogenous (P < 0.001).

Discussion

Graphs 2 and 3 demonstrate that enrofloxacin effectively treats respiratory tract infections in pigs (P < 0.001), and that in the enrofloxacin groups there were fewer deaths (P = 0.037).

In the study of efficacy and from graph 4 (funnel plot), we established that there was a heterogeneity of included studies, therefore, the total effect size was also calculated according to the random model.

The reasons for heterogeneity might probably be explained in terms of the larger number of included studies which dealt with different respiratory tract infections and were compiled in the joint meta-analysis, along with different sample sizes in individual studies. The susceptibility analysis, which excluded the four studies which stood out from the rest (17, 30; 32, 58,), demonstrated that these studies were not the cause of heterogeneity.

The causative pathogens are also characterized by a considerably low resistance of all bacteria that cause respiratory tract infections whereas the high efficacy of enrofloxacin is indicated by the low MICs of bacteria which are the causative pathogens of respiratory tract infections (Table 2. and 3.)

As it is so effective in treating PRDC, usage of enrofloxacin has benefits also regarding economic

parameters: eg. gain of animals, feed conversion ratio, mortality ect. in all reviewed trials where these parameters were examined.

The cause of vaccine failure is often unknown, and requires deeper understanding of the pig immune system, pathogenesis of the microbe and other potential factors (early weaning, multisite and age segregated systems, increased size of units and numbers of sourcing farms).The use of antimicrobials for control for PRDC remains still necessary in addition with other management strategies: balanced and stable sow herd, biosecurity to prevent the spread and introduction of disease, reduction of stress, optimal stocking density, ventilation, air quality etc.

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METAANALIZA IN SISTEMATIČNI PREGLED UČINKA ENROFLOKSACINA NA PRAŠIČJI RESPIRATORNI BOLEZENSKI SINDROM (PRDC)

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Povzetek. Prašičji respiratorni bolezenski sindrom (angl.: porcine respiratory disease complex - PRDC) je ekonomsko pomembna motnja. Zanj je značilna večja smrtnost živali, manjši dnevni prirast, zmanjšan apetit, daljše pitanje živali, kašelj, težko dihanje, pljučnica. Metaanaliza je metoda pregledovanja in kombiniranja rezultatov, dobljenih v različnih neodvisnih kliničnih poskusih. Sistematični pregledi so kratki povzetki najboljših dosegljivih dognanj na natančno definirana vprašanja. Poskušajo zbrati in pregledati vse kakovostne podatke o obravnavani temi. To vključuje obširno iskanje vseh potencialno pomembnih člankov in uporabo jasno ponovljivih kriterijev pri izboru študij, uporabljenih za pregled. Enrofloksacin je fluorokinolonski kemoterapevtik, ki so ga razvili izključno za rabo v veterinarski medicini. Celotni rezultati metaanalize kažejo na visoko učinkovitost enrofloksacina ($P < 0,001$) pri zdravljenju PRDC. Smrtnost je bila manjša v skupinah, zdravljenih z enrofloksacinom ($P = 0,037$). Odpornost proti vsem bakterijam, ki povzročajo okužbe dihal, je bila nizka (0 % - 7,6 %). Z metaanalizo in sistematičnim pregledom smo dokazali visoko učinkovitost enrofloksacina pri PRDC in njegovo ekonomsko korist.

Ključne besede: fluorokinoloni; metaanaliza; prašiči; prašičji respiratorni bolezenski kompleks