Mycoplasma hyopneumoniae infections in pigs: update on epidemiology and control

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Introduction

Mycoplasma hyopneumoniae (M. hyopneumoniae) is the primary pathogen of enzootic pneumonia (EP), a chronic respiratory disease in pigs resulting from combined infections with M. hyopneumoniae and one or more secondary bacterial pathogens (Thacker, 2006). M. hyopneumoniae is also one of the primary agents involved in the porcine respiratory disease complex (PRDC). This respiratory complex includes both bacterial (Actinobacillus pleuropneumoniae, Pasteurella multocida, streptococci) and viral (porcine reproductive and respiratory syndrome virus (PRRSV), porcine circovirus type 2 (PCV2), Aujeszky’s disease virus, swine influenza viruses (SIV) and porcine respiratory coronavirus) agents (Sibila et al., 2009). Both disease conditions cause major economic losses to the swine industry mainly due to reduced growth rate, poor feed conversion ratio, increased medication costs and increased mortality (Maes et al., 1996). Since elimination of M. hyopneumoniae from infected herds is difficult to achieve and also to maintain, most efforts are currently directed towards control of the disease. In the present paper, first some aspects of the epidemiology of M. hyopneumoniae infections will be reviewed, next interactions with other respiratory pathogens will be discussed, and finally an update will be given on control strategies.

Transmission of M. hyopneumoniae

Within a herd, M. hyopneumoniae is normally transmitted to susceptible pigs by direct contact with infected pigs or by sharing the same air-space with infected pigs. Piglets can become infected already in the farrowing unit by the sow either by direct nose-to-nose contact or by aerosols (vertical transmission). The chance of transmission from sow to offspring is higher in gilts and low parity sows (Fano et al., 2006), but also older sows (Pieters et al., 2009) showed that pigs can remain infectious for a distance of 3.2 km. Dee et al. (2004) found that during the nursery period, one infected pig will infect at least one penmate (Table 1). In the same study, it was also shown that the transmission rate tended to be higher with a highly virulent M. hyopneumoniae isolate than with a low virulent isolate (Vicca et al., 2003), but the difference was not statistically different. Villarreal et al. (2010a) found slightly lower transmission rates in pigs during the same period under field conditions. Morris et al. (1995) showed that pigs being in direct contact with other infected pigs are 7 times more likely to seroconvert than those having indirect contact.

Table 1. Results of transmission experiments of M. hyopneumoniae in nursery pigs (4-10 weeks old). Two out of 8 piglets were experimentally infected at the start of the experiment and the number of infected pigs was investigated 6 weeks later. Transmission rates are expressed using adjusted reproduction ratios (Rn) values (Meyns et al., 2004)

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<tr>
<td># of infected animals / # of susceptible animals</td>
<td>2/6</td>
<td>3/6</td>
<td>5/6</td>
<td>2/6</td>
<td>2/6</td>
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<tr>
<td>Rn = 1.47 (0.68-3.38)</td>
<td>Rn = 0.85 (0.33-3.39)</td>
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The transmission of M. hyopneumoniae between herds can take place either by trade of (subclinically) infected pigs or by airborne transmission. The importance of airborne transmission has been illustrated in many field studies. Goodwin (1985) concluded that EP-free herds could be reinfected by airborne transmission of M. hyopneumoniae over a distance of 3.2 km. Dee et al. (2009) have recently shown that airborne transport of M. hyopneumoniae organisms occurred out to a distance of 4.7 km. Apart from direct contact and airborne transmission, indirect transmission of infection through fomites is not considered to be important.

Interactions of M. hyopneumoniae with other pathogens

The interaction of M. hyopneumoniae with other pathogens has received much attention. In the past, studies mainly focussed on
the interaction with parasitic and bacterial infections, whereas recently, the emphasis has been shifted towards the interactions with viral infections.

Parasitic pathogens
Lesions typical for EP are more severe in *M. hyopneumoniae* infected pigs that are concurrently infected with parasites such as *Metastrongylus elongatus* or *Ascaris suum*. *Flejsa and Ulvesaeter* (1980) reported that the extent of pneumonia was associated with the presence of liver lesions due to migrating *A. suum* larvae. Other studies reported that the prevalence of pneumonia in a herd was positively associated with the prevalence of liver lesions in the herd. *Steenhard et al.* (2009) showed that experimental infections with *A. suum* may significantly compromise the immune response following *M. hyopneumoniae* vaccination.

Bacterial pathogens
*M. hyopneumoniae* predisposes pigs to infections with secondary bacteria. Different mechanisms may be involved in this phenomenon: damage of the epithelium, induction of caving lesions (massive infiltration of lymphohistiocytic cells), induction of thick, viscous mucus, and modulation of the immune system. Combined experimental infections with *M. hyopneumoniae* and either *Pasteurella multocida* (Sørensen et al., 1997) or *Actinobacillus pleuropneumoniae* (Marois et al., 2009) result in more severe lesions compared to the single infections. Co- or subsequent infections with *P. multocida* and *A. pleuropneumoniae*, and with other bacteria such as *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Arcanobacterium pyogenes*, streptococci or staphylococci are commonly found in field outbreaks of EP. Different studies are inconsistent as to whether there is an association between turbinate atrophy and pneumonia.

Viral pathogens
Initial studies focussing on the interaction between *M. hyopneumoniae* and PRRSV could not demonstrate a potentiating effect of both pathogens (Van Alstine et al., 1996). Some years later however, it was shown under experimental conditions that *M. hyopneumoniae* significantly prolonged and increased the severity of PRRSV-induced pneumonia (Thacker et al., 1999). Dual infection studies with *M. hyopneumoniae* and SIV could not show the potentiating effects of both pathogens as observed with PRRSV. The effect was less pronounced and only transitory. *Opriessnig et al.* (2004) indicated using an experimental study that *M. hyopneumoniae* infection potentiates the severity of PCV2-associated lung and lymphoid lesions, increases the amount and prolongs the presence of PCV2-antigen, and increases the incidence of PMWS in pigs. On the contrary, the different experiments using dual infections with *M. hyopneumoniae* plus either PRRSV, SIV or PCV2 could not demonstrate a virus-dependent enhancement of mycoplasmal pneumonia. Combined infections under standardised experimental conditions may provide very useful information on the interactions of pathogens, but they only partially reflect the complexity of PRDC as occurring under field conditions. Many different pathogens may be involved under field circumstances, and environmental conditions such as management, breed and immunity of the animals, housing and air quality may largely influence the infection and disease course.

Control of *M. hyopneumoniae* infections

Optimization of management practices and housing conditions
Optimizing management and housing conditions is primordial in the control of *M. hyopneumoniae* infections and should be the first to be accomplished. Instituting management changes that reduce the possibilities of spreading *M. hyopneumoniae* or result in decreased lung damage by other pathogens may significantly improve the control of enzootic pneumonia. Additional factors different from housing and management conditions, such as strain differences, may determine the infection pattern and clinical course of the disease (Vicca et al., 2002). An overview of control measures for *M. hyopneumoniae* infections related to environmental and management factors has been published by *Maes et al.* (2008).

Antimicrobial medication
To control and treat respiratory disease including *M. hyopneumoniae* infections in pigs, tetracyclines and macrolides are most frequently used. Also, other potentially active antimicrobials against *M. hyopneumoniae* include lincosamides, pleuromutilins, fluoroquinolones, florfenicol, aminoglycosides and aminocyclitols. Fluoroquinolones and aminoglycosides have mycoplasmacidal effects. Since the organism lacks a cell wall, it is insensitive to β-lactamic antibiotics such as penicillins and cephalosporins. Although acquired antimicrobial resistance of *M. hyopneumoniae* has been reported to tetracyclines (Inamoto et al., 1994), and recently also to macrolides, lincosamides and fluoroquinoles (Vicca et al., 2004), it does not seem to constitute a major problem for treatment of *M. hyopneumoniae* infections to date.

An overview of peer reviewed studies assessing the efficacy of various antimicrobials used against *M. hyopneumoniae* infections under experimental as well as under field conditions is given by *Vicca* (2005). It can be concluded that for most antimicrobials tested, performance parameters were improved and lung lesions as well as clinical signs were decreased in treated animals. Treatment and control of enzootic pneumonia outbreaks may be disappointing because the symptoms may reappear after cessation of the therapy. Pulse medication in which medication is provided intermittently during critical production stages of the pigs, can also be used (Le Grand and Kobish, 1996). Pulse medication during extended periods of time as well as continuous medication during one or more production stages should be discouraged because of both the increased risk of spread of antimicrobial resistance and the possible risk for antimicrobial residues in the pig carcasses at slaughter.

In endemically infected farms, strategic medication of the reproductive herd is sometimes practiced as an attempt to decrease the bacterial shedding from sows to the newly introduced gilts. Antimicrobial medication of recently weaned pigs has been shown to reduce the number of *MM. hyopneumoniae* organisms in the respiratory tract (Vicca et al., 2005; Thacker et al., 2006), but further research is necessary to quantify the shedding of *M. hyopneumoniae* organisms in sows receiving antimicrobial medication.

Vaccination

Commercial vaccines
Commercial vaccines, consisting of inactivated, adjuvanted whole-cell preparations, are widely applied worldwide. The major advantages of vaccination include improvement of daily
weight gain (2-8%), feed conversion ratio (2-5%) and sometimes mortality rate. Additionally, shorter time to reach slaughter weight, reduced clinical signs, lung lesions and lower treatment costs are observed (Maes et al., 1998, 1999). Although protection against clinical pneumonia is often incomplete and vaccines do not prevent colonization, some studies indicate that the currently used vaccines may reduce the number of organisms in the respiratory tract (Meyns et al., 2006) and may decrease the infection level in a herd (Sibila et al., 2007). Transmission studies under experimental (Meyns et al., 2006) and field (Villarreal et al., 2010a) conditions showed that vaccination against M. hyopneumoniae with commercial vaccines induced only a limited and non-significant reduction in the spread of M. hyopneumoniae. Consequently, vaccination alone with the current vaccines will not be sufficient to eliminate M. hyopneumoniae from infected pig herds.

**Vaccination strategies**

Different vaccination strategies have been adopted, depending on the type of herd, the production system and management practices, the infection pattern and the preferences of the pig producer. Moreover, under field conditions, optimal vaccination strategies must balance the advantage of delayed vaccination with the need to induce immunity before exposure to pathogens. Since infections with M. hyopneumoniae may already occur during the first weeks of life, vaccination of piglets is most commonly used. Its efficacy has been demonstrated by means of numerous studies under experimental as well as field conditions (Jensen et al., 2002). Vaccination of suckling piglets (early vaccination; < 4 weeks of age) is more common in single-site herds, whereas vaccination of nursery/early fattening pigs (late vaccination; between 4 and 10 weeks) is more often practiced in three-site systems where late infections are more common.

Traditionally, double vaccination was the most frequent practice. During the last years, one-shot vaccines have been shown to confer similar benefits as two-shot vaccines and are more often used now (Baccaro et al., 2006). One-shot vaccination is especially popular because it requires less labor and it can be implemented more easily in routine management practices on the farm.

Vaccination of suckling piglets has the advantage that immunity can be induced before pigs become infected, and that less pathogens are present that can interfere with immune response. Possible disadvantages of vaccinating piglets before weaning include the presence of maternal antibodies and an increased risk for more severe PCV2 infections after weaning.

Vaccination of nursery pigs has no or less interference with possible maternally derived antibodies. However, nursery pigs may already be infected with M. hyopneumoniae. In addition, the age of infection or the age-window in which the piglets become infected may vary between successive groups within a herd (Sibila et al., 2004). Finally, many infections such as PRRSV or PCV2 mainly take place after weaning and may affect the general health status of the pigs, and consequently also interfere with proper immune responses after vaccination.

Only a few studies have assessed the effects of sow vaccination. Vaccination of sows at the end of gestation aims to both reduce the shedding of M. hyopneumoniae from the sow to the offspring and to protect the piglets against infection via maternally-derived immunity. It has been shown that vaccinating sows 5 and 3 weeks before farrowing was associated with a lower number of positive piglets at weaning using nested PCR on nasal swabs, both in farrow-to-finish operations and multisite production systems (Sibila et al., 2008). However, maternally derived antibodies only provide partial protection against lesion development and provide limited to no effect on colonization of M. hyopneumoniae (Thacker et al., 2000). The role of antigen-specific maternally derived immune cells in protection against M. hyopneumoniae is not known. Bandrick et al. (2006) showed in vivo response by delayed-type hypersensitivity and in vitro proliferation of maternally derived cells when newborn piglets were stimulated with M. hyopneumoniae antigen. Since piglets from vaccinated sows can still be infected, additional measures to control M. hyopneumoniae during the nursery and finishing phases may be warranted.

Vaccination of gilts is recommended in endemically infected herds to avoid destabilization of breeding stock immunity (Bargen et al., 2004). This is particularly the case when gilts are purchased from herds that are free from M. hyopneumoniae or from herds with a low infection level of M. hyopneumoniae. Although vaccination confers beneficial effects in most infected herds, the effects are variable between herds. The variable results may be due to different factors such as improper vaccine storage conditions and injection technique, antigenic differences between field strains and vaccine strains, presence of disease at the time of vaccination, and interference of vaccine induced immune responses by maternally derived (colostral) antibodies.

**Experimental vaccines**

Investigation of new vaccines is actively occurring, including the use of aerosol and feed-based vaccines as well as subunit and DNA vaccines (Fagan et al., 2001; Lin et al., 2003; Murphy et al., 1993). Intradermal vaccination with a commercial bacterin has been shown to be efficacious (Jones et al., 2004). If M. hyopneumoniae vaccines could be delivered to the animals via aerosols or via the feed, this would provide an easy means for mass vaccination since it would substantially reduce labor costs and it would also be better for the welfare of the pigs as well as for stimulating a mucosal immune response at the respiratory tract. However, aerosol vaccination given 3 times with 2 weeks interval provided insufficient protection, in contrast with the intramuscular application of the same commercial vaccine which was efficacious (Murphy et al., 1993). On the other hand, Lin et al. (2003) showed that an oral micro-spheres experimental vaccine based on the PRIT-5 M. hyopneumoniae strain and prepared by a co-spray drying method significantly reduced pneumonia lesions following challenge infection with M. hyopneumoniae in pigs.

King et al. (1996) found only minimal and non-significant protection in a pig challenge infection model using a recombinant subunit vaccine based on the P97 adhesin of M. hyopneumoniae. Intranasal immunization of pigs with the attenuated Erysipelothrix rhusiopathiae YS-19 strain expressing a recombinant protein of M. hyopneumoniae P97 adhesin significantly reduced the severity of pneumonic lung lesions following challenge infection (Shimoji et al., 2003). However, apparently significant immune responses were not observed in the immunized pigs. Oral administration of the same recombinant protein in another live strain of E. rhusiopathiae (Ogawa et al., 2009) significantly reduced the severity of pneumonic lung lesions. Okamba et al. (2007) showed that a replication-defective adenovirus expressing the C-terminal portion of M. hyopneumoniae-P97 adhesin applied intranasally and intramuscularly in BALB/c mice, induced
significant immune responses. Also several experimental DNA-vaccines have been developed and tested for immune responses in mice or pigs. Significant immune responses with DNA-vaccines were elicited in mice, based on the expression of a heat shock protein gene P42 (Chen et al., 2003), a ribonucleotide reductase R2 subunit gene fragment of *M. hyopneumoniae* (Chen et al., 2006), or the expression of different genes coding for several potential protective antigens (P36, P46, NrdF, P97, P97R1) (Chen et al., 2008). The studies suggest that these vaccines may represent new strategies for controlling *M. hyopneumoniae* infections in pigs, but they need to be validated in pigs under experimental and practical circumstances. Villarreal et al. (2009) showed that pigs inoculated with low virulent isolates of *M. hyopneumoniae* are not protected against a subsequent infection with a highly virulent *M. hyopneumoniae* isolate 4 weeks later and may even develop more severe disease signs. This may indicate that subsequent infections with different *M. hyopneumoniae* isolates may lead to more severe clinical disease in a pig herd.

Further studies are necessary for improving vaccines and vaccination strategies. From an immunological point of view, challenges include induction of immunity at the mucosal level. For rational design of vaccines, a comprehensive understanding of the pathobiology of *M. hyopneumoniae* infections and the molecular basis of pathogenicity of this micro-organism is required. Bacterial genes and antigens involved in survival of the bacterium in the host or that render the bacterium harmful to the host need to be identified. This may be facilitated by the fact that the genome of 3 different *M. hyopneumoniae* isolates has been sequenced (Minion et al., 2004; Vasconcelos et al., 2005).

**Preventive medication versus vaccination**

The use and efficacy of either vaccination or preventive (strategic) medication has been frequently discussed and the question arises whether medication and/or vaccination should be used. Advantages and disadvantages of both strategies are given in Table 2. Antimicrobials can be used in a flexible way, they are often effective against several (respiratory) pathogens and their administration is less labor-intensive since in-feed or in-water medication is mostly used. Vaccination, on the other hand, does not select for antimicrobial resistance in pathogenic bacteria and in bacteria belonging to the microbiota of the animal. It also avoids risks for antimicrobial residues in the pig carcasses at slaughter. While an immediate effect can be expected for antimicrobial treatment, the effect of vaccination of young piglets will only be evident at herd level if it is practiced for at least several months. Although vaccines are directed towards control of *M. hyopneumoniae* infections, also other secondary bacterial infections (Pasteurella multocida, Actinobacillus pleuropneumoniae) or lung lesions caused by these pathogens less frequently occur after vaccination (Maes et al., 1998; 1999; Meyns et al., 2006). In addition, it is very likely that combined vaccines will be used more frequently in the future. In this way, vaccination against different respiratory pathogens will be possible using one single application.

Neither vaccination nor preventive medication can prevent infection and adherence of *M. hyopneumoniae* to the ciliated cells of the respiratory tract (Le Grand and Kobisch 1996). Finally, in case of high infection levels and/or in herds with poor management and housing conditions, the use of antimicrobials may remain necessary or may confer additional clinical and performance benefits in vaccinated herds (Mateusen et al., 2002).

### Table 2. Comparison between vaccination and antimicrobial medication for the control of *M. hyopneumoniae* infections

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<tr>
<th>Parameter</th>
<th>Vaccination</th>
<th>Antimicrobial medication</th>
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<tr>
<td>Strategy for use on farm</td>
<td>Long term</td>
<td>More flexible</td>
</tr>
<tr>
<td>Labor</td>
<td>More laborious</td>
<td>Less laborious</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Against one pathogen</td>
<td>Against different pathogens (e.g. multiple disease challenges)</td>
</tr>
<tr>
<td>Risk for residues</td>
<td>No</td>
<td>Yes (inappropriate use)</td>
</tr>
<tr>
<td>Risk for antimicrobial resistance</td>
<td>No</td>
<td>Yes (inappropriate use)</td>
</tr>
<tr>
<td>Prevention of colonization</td>
<td>No</td>
<td>No</td>
</tr>
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### Conclusions

*M. hyopneumoniae* infections occur worldwide and may affect pigs in various types of pig herds. The infection pattern, clinical course, the lung lesions and ultimately the financial losses vary largely depending on the herd, the management practices, the housing conditions, and also on the interactions between different respiratory pathogens. Control measures include optimizing management practices and housing conditions, the use of medication and vaccination. These measures can decrease the infection level in a herd and the number of organisms in the lungs, and improve health conditions of the animals but they do not guarantee the absence of *M. hyopneumoniae*. Further efforts are needed for development of more effective vaccines and vaccination strategies.

### References


