Chapter 3

Viral Kinetics, Shedding Profile and Transmission of Serotype 1 Marek's Disease Vaccine Rispens/CVI988 in Maternal Antibody-free Chickens

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Chapter 4

Replication kinetics and shedding of very virulent Marek's Disease virus and vaccinal Rispens/CVI988 virus during single and mixed infections varying in order and interval between infections

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Chapter 5

Vaccination-challenge interval markedly influences protection provided by Rispens/CVI988 vaccine against very virulent Marek's disease virus challenge

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6 General discussion and conclusions

The most important purpose of the research undertaken in this thesis was to use a new molecular diagnostic test, which differentiates between wild type and Rispens/CVI988 serotype 1 Marek's disease virus (Rispens/CVI988) to investigate the kinetics of viral replication and persistence within the host, and shedding pattern, of the Rispens/CVI988 virus alone and in combination with wild type virus. These objectives were successfully realized and contribute to an improved understanding of the kinetics, shedding and transmission of the Rispens/CVI988 virus in chickens, the effect of different vaccination to challenge intervals on protection provided by the Rispens/CVI988 vaccine and interaction between Rispens/CVI988 and pathogenic MDV-1 in the same host.

While comprehensive discussion has been provided in the relevant chapters of the thesis, this section will review the main findings in an integrated way and discuss the implications of the work.

6.1 Kinetics and shedding of Rispens/CVI988 in vaccinated chickens (single infection)

From the first experiment we found that Rispens/CVI988 load in PBL was highest at the first measurement at 7 dpc, declining by about 1 log to day 21 with a further 1.5 logs decline between days 42 and 56. The pattern was a bit different in the second experiment where the Rispens/CVI988 load in PBL increased from 7 dpv to 14 dpv then plateaued until 28 dpv, before increasing slightly until 42 dpv where the viral load peaked. When Rispens/CVI988 loads were low, it was usually due to the presence of many negative samples, and when only positive samples were analysed, the viral load over time varied little and lay between 3 to 4 logs in both experiments. In experiment 1 the viral load in feather tips peaked later (14 dpv) than for PBL and then declined by approximately 1 log per week until day 42 before increasing slightly at 56 dpv. In experiment 2 Rispens/CVI988 load in feather increased to the last measurement at 21 dpv but the viral load was similar to the 21 dpv Rispens/CVI988 load

of first experiment. Baigent *et.al*. (2005b) reported the presence of the virus in both PBL and feather tips at 4 dpv with numbers increasing to a peak at 14 dpv before gradually decreasing until the last day of their experiment at 28 dpv. Haq *et al.* (2012) also reported the same pattern in feather tips.

The results of both experiments showed that Rispens/CVI988 is shed readily from vaccinated chickens into the environment in large amounts, and was detected readily in dust samples from day 7 onwards. In experiment 1 all dust samples tested positive at 7 dpv and Rispens/CVI988 load in dust peaked at day 21, then plateaued at around 5 logs until 56 dpv. The pattern was somewhat different in experiment 2 where Rispens/CVI988 load peaked at 42 dpv and then plateaued around 5 logs. This pattern is very similar to the shedding pattern of pathogenic MDV-1, MDV-2 and HVT (Islam and Walkden-Brown, 2007b). Though the Rispens/CVI988 load was nearly 1.5 logs and 2 logs lower than reported for pathogenic MDV-1 and MDV-2 respectively.

6.2 Transmission of Rispens/CVI988 vaccine

Rispens/CVI988 transmitted very effectively from vaccinated chickens to in-contact unvaccinated chickens with a lag period of 2 - 3 weeks. In PBL, 93 % of vaccinated birds were positive for MDV-1 at 7 dpv rising to 100 % by day 28 while, for the in-contact birds, 38 % were positive at day 21 (first sampling) rising to 96.3 % by 56 dpv. In feather tips, 83 % of vaccinated birds were positive for MDV-1 at 7 dpv rising to 100 % by 14 dpv while for the in-contact birds, 72 % were positive at day 21, rising to 100 % by 28 dpv. The pattern of Rispens/CVI988 viral load in feather tips was similar in in-contact chickens but with a lag of about two weeks (1st experiment). This was less apparent for PBL in which the lag was closer to 3 weeks. Viral load in both PBL and feather tips was higher in in-contact birds than vaccinated birds at an equivalent point post infection but no significant difference was found in viral load of spleen at 56 dpv and antibody titre.

Rispens *et al*., (1972a) reported that at a passage level of 35 the virus spread directly to contact chickens as determined by virus isolation and antibody levels. However, a plaque purified clone of CVI988 named CVI988/C with passage level of 65 (De boer*, et al.*, 1986)

showed only limited transmission to in-contact chickens (0/8 by virus isolation and 4/10 by serology) (Witter, *et al.*, 1987) and CVI988 with an initial passage level of 42 showed inefficient transmission to in-contact chickens (Witter, *et al.*, 1995). The passage level of current commercial vaccine strains is confidential, but given that CVI988 seed was made available to vaccine companies at passage level 33 (van Iddekinge, *et al.*, 1999) it is a reasonable inference that currently used vaccine strains have a passage level in the range of 35 - 45.

These results suggest that the ability of CVI988 to transmit is negatively associated with passage level in cell culture. Possibly the level of *in vivo* replication at higher passage levels is below the threshold level required for efficient shedding. Alternatively the higher passage viruses may contain mutations that restrict their ability to shed and/or infect in-contact chickens.

As the Rispens/CVI988 virus transmitted effectively from vaccinated to contact chickens and there was no significant effect of pathogenic MDV challenge on Rispens/CVI988 shedding if challenge followed vaccination it could be possible that the Rispens/CVI988 virus has escaped in the environment and is competing with wild-type MDV, thus also influencing in the shedding of pathogenic MDV in the environment. Evidence of such interaction between low or avirulent MDV and pathogenic MDV in the field has been reported previously (Jackson, *et al.*, 1976).

6.3 Protection and vaccination challenge interval

VCI had a major effect on the level of protection provided by Rispens/CVI988 against vvMDV. The PI values for VCI 0, VCI 5 and VCI 10 were 60.4 %, 84.8 % and 100 % respectively with a highly significant positive linear association between PI and VCI on an individual isolator basis. On the other hand no significant protection occurred if challenge preceded vaccination by 5 (VCI -5) or 10 (VCI -10) days. It has been shown that vaccination of maternal anti MDV antibody-positive broilers with a range of HVT doses induced higher protection against MDV challenge at a VCI of 5 (mean PI of 79 %) than a VCI of 2 (mean PI of 15 %) (Islam, *et al.*, 2007a). Islam *et al.* (2008) reported a PI of HVT vaccination against

MDV challenge in maternal antibody-positive broilers of 48, 69 and 77 % for VCI of 2, 4 and 7 days respectively. In a second experiment they reported PI of 66, 33, 53, 76 and 76 % for VCI of 0, 2, 4, 7 and 10 days respectively, concluding that for HVT, no improvement in protection is obtained beyond a VCI of 7 days. In all studies using maternal antibody-positive chickens those with longer VCI are challenged later, and thus have lower levels of maternal antibody directed against MDV at challenge time than those with shorter or negative VCI. It is established that the presence of maternal antibody directed against MDV slows the pathogenesis of MD (Chubb and Churchill, 1969), presumably by slowing the MDV replication rate. It is therefore possible that part of the observed effect of VCI is mediated by a reduced maternal antibody (passive immunity) inhibition of challenge virus, in addition to the enhanced active immunity expected when the immune response has had time to develop.

Our data suggest that maximal protection against vvMDV is obtained by day 10 following vaccination with Rispens/CVI988. This is consistent with the report of Baigent *et al.,* (2007) that chickens vaccinated with Rispens/CVI988 at day old followed by challenge with MDV at 14, 21 and 28 days post vaccination exhibited consistently high levels of protection (> 90%). The comparative efficacy of the Rispens/CVI988 vaccine appears to be high as well. Renz (2008) reported a PI of 27.2 and 63.1 % for HVT and HVT/SB1 vaccines administered to ISA Brown chicks at hatch, followed by challenge with 500 pfu of 02LAR at day 5 (VCI = 5). This compares with a value of 85 % for VCI 5 in the present experiment.

This study also showed that 56 dpi antibody titres were significantly higher than the 21 dpi titres in all treatments indicating an active response to infection, and the likely initial inhibitory effect of maternal antibody directed against MDV. There was also a broadly positive relationship between antibody titre and VCI and thus with PI. Interestingly, administration of pathogenic MDV in addition to the Rispens/CVI988 vaccine virus generally reduced antibody titres, except at a VCI of 10. This suggests that pathogenic MDV interferes with the immune response to Rispens/CVI988 vaccination.

In summary, results from the protection experiment support the widely held view that the Rispens/CVI988 vaccine is probably the most effective vaccine against MDV currently available. However, for optimum protection against MD using the Rispens/CVI988 vaccine,

the VCI should be not less than 10 days. In the field it is very hard to control this but by routine monitoring of the virus levels in the previous flock and following strict biosecurity practices it may be possible to extend the time to first significant challenge after vaccination. Given the negligible reported incidence of MD in Rispens/CVI988 vaccinated chickens, it appears that under most circumstances this is achieved currently.

6.4 Effect of mixed infection on kinetics

In Experiment 2 we investigated the kinetics and shedding profile of a very virulent MDV-1 (02LAR) and vaccinal MDV-1 (CVI988/Rispens) when chickens were coinfected at different VCI. The results indicated that effects of both viruses on each other were highly dependent on VCI and similar in nature.

Vaccination with Rispens/CVI988 reduced the viral load of pathogenic MDV significantly in PBL, feather cells and dust when the birds were vaccinated at hatch and challenged 5 days (VCI 5) and 10 (VCI 10) after vaccination but not when vaccination and challenge were concurrent (VCI 0). Moreover the reduction was greatest with the longest VCI. When VCI was 5 days or 10 days reduction was 3 - 5 logs respectively in PBL, 2.5 - 5 logs in feather cells, 1 - 2 logs in dust. Similar but smaller reductions were observed in positive PBL and feather cell samples but not in positive dust samples. However the pattern of pathogenic virus in PBL, feather cells and dust was similar in single and mixed infected birds over time and was broadly similar when all samples were analysed or only positive samples. Haq *et al*. (2012) showed that Rispens/CVI988 reduced pathogenic MDV genome load by 1 log in feather cells of coinfected chickens where chickens were vaccinated *in ovo* and challenged at 5 days of age. These findings are consistent with the effects of other vaccine viruses. For example Islam *et al*. (2008) showed that HVT vaccination significantly reduced pathogenic MDV load in dust and the reduction was greatest for treatments with the longest VCI.

Challenge with pathogenic MDV reduced the Rispens/CVI988 viral load highly significantly in PBL and feather cells but not in dust when the birds were challenged at hatch and vaccinated at 5 days and 10 days after challenge. However, when vaccination and challenge were concurrent (VCI 0) or vaccination preceded challenge no significant reduction occurred.

Moreover, there was no significant reduction observed when only positive samples were analysed. The pattern of Rispens/CVI988 virus load in PBL, feather cells and dust over time was similar in single and mixed infected birds. Similar overall patterns were seen when only positive samples were included. Baigent *et al.* (2011) and Haq *et al*. (2012) found that challenge with pathogenic MDV-1 had no significant effect on the mean level of BAC-cloned CVI988 and CVI988 respectively in feather cells, presumably because in their studies vaccination preceded challenge. However, it has been shown for the MD vaccine viruses HVT and MDV-2 that challenge with pathogenic MDV following vaccination enhances both replication and subsequent shedding in dust (Islam and Walkden-Brown, 2007b). However, in the present study, this was not observed for the Rispens/CVI988 virus, perhaps reflecting a basic difference between the MDV serotypes.

So, in our study we have found that vaccination with Rispens/CVI988 prior to challenge reduces pathogenic MDV load, and vvMDV challenge prior to vaccination also reduces Rispens/CVI988 MDV load in PBL and feather cells. However, there was no similar interactive effect of the viruses on the MDV load in dust though the pathogenic MDV shedding pattern was different between unvaccinated and vaccinated chickens. However, challenge with pathogenic MDV has little or no effect on shedding of Rispens/CVI988 virus in dust.

6.5 Prediction of vaccinal success and protection

There was a strong positive association between Rispens/CVI988 load in PBL and feather tips. Both of these at day 56 were also significantly associated with Rispens/CVI988 load in spleen. On the other hand, there was no overall association between MDV load in weekly dust samples and that in PBL or feathers. This suggests that the extracted DNA from feather tips may be more representative of leucocytes in the feather pulp, than of dander. This contrasts with the close association between MDV load in feather tips and dust reported recently (Baigent*, et al.*, 2013).

There was a significant positive association between anti MDV antibody titre on day 56 and Rispens/CVI988 load in PBL on days 7, 28, 35, 42, 49 and 56. However, earlier measures of

MDV load in feathers and dust were not significant predictors of anti MDV antibody titre on day 56. The correlation between the level of anti-MDV antibody at day 56, and the level of replication of CVI988 in PBL, would suggest that greater replication of CVI988 will lead to induction of a greater anti-MDV immune response. This in turn would support the administration of a full commercial dose of vaccine to obtain maximum protection.

Pathogenic MDV viral load in PBL and feather tips at 14 and 21, but not 7, dpc were good predictors of subsequent MD incidence in experiment 2, whereas the load of Rispens/CVI988 in the same samples was not. Other studies have shown that the load of MDV in lymphocytes or splenocytes in the first few weeks after challenge are good predictors of subsequent MD status (Gimeno*, et al.*, 2008; Islam*, et al.*, 2008; Islam*, et al.*, 2007a; Islam*, et al.*, 2006b; Walkden-Brown*, et al.*, 2013b) but that the load of HVT is not (Gimeno*, et al.*, 2008; Islam*, et al.*, 2006b). In the case of isolator exhaust dust no significant association were found between either pathogenic MDV-1 or Rispens/CVI988 virus on subsequent MD incidence in experiment 2. This contrasts with the findings of Walkden-Brown *et al*. (2013b) who showed that MDV load in dust at 14 and 21 dpc were powerful early predictors of subsequent MD status in commercial broiler chickens. The reasons for this difference are not clear.

The findings of experiment 1 study suggest that measuring Rispens/CVI988 in dust is most practical for monitoring Rispens/CVI988 vaccine take, as Rispens/CVI988 viral load was consistently high in dust between 7 and 56 dpv. Dust samples also have the advantage of integrating information from a large number of chickens so fewer measurements are required, and being easier to collect, transport and store than other tissues which require a cold chain between the farm and the laboratory (Walkden-Brown*, et al.*, 2013a).

6.6 Application of findings

The main practical applications of the findings of this doctoral thesis are summarised below.

1. Successful transmission of the Rispens/CVI988 virus means that, provided challenge is late, partial vaccination failure may have less severe consequences as chickens will acquire the vaccine virus from flock mates. Furthermore under experimental conditions, the Rispens/CVI988 vaccinated birds must be kept separate from

unvaccinated chickens unless natural transmission of Rispens/CVI988 to in-contact chickens is desired.

2. Rispens/CVI988 vaccination success can be measured by using qPCR tests that differentiate between Rispens/CVI988 and pathogenic MDV. The preferred sample material is dust due to representing a population of chickens, ease of collection, transportation and storage relative to feathers and soft tissues. Rispens/CVI988 load in dust is most reliable for monitoring Rispens/CVI988 vaccine efficacy, as Rispens/CVI988 viral load is peaked at 21 dpv and is consistently higher in dust than other tissues from day 7 until day 56.

3. To predict subsequent MD incidence under conditions where challenge is high pathogenic MDV load in PBL and feather tips at 14 and 21 dpc were the best predictors.

4. Defining the kinetics and shedding profiles of Rispens/CVI988 and pathogenic MDV in the same host when the viruses are administered in different order at different intervals will enable improved modelling of the effects of vaccination on fitness of wild-type MDV and evolution of virulence in the latter.

5. As Rispens/CVI988 reduced the viral load and shedding of pathogenic MDV in chickens vaccinated prior to challenge, it is effectively reduced the reproductive efficiency of pathogenic MDV. As virulence in pathogenic MDV is positively associated with MDV replication rate and shedding (Atkins *et al.*, 2011) such vaccination would favour reproductive success of more virulent strains with higher replication rates. This is particularly true as vaccination mostly prevents early death of the host due to challenge (Ch. 5), which is the main evolutionary constraint to increasing virulence. Thus the kinetic and protection studies of Chapters 4 and 5 support the notion that vaccination with imperfect vaccines would favour evolution towards increasing virulence as postulated by Gandon et al., (2001).

6.7 Future work

The findings of this thesis inevitably raise potential new areas of investigation, some of which are summarised below.

1. We measured the transmission of Rispens/CVI988 in SPF chickens not containing anti-MDV antibody, which is not typical of field conditions. For this reason it would be good to investigate transmission between commercial chicks, which invariably contain maternal antibody directed against MDV. This may slow the rate of transmission of the virus.
2. We artificially challenged and vaccinated the birds with pathogenic and vaccinal MDV-1 to find out how they interact with each other. It would be interesting to know how efficiently the viruses transmit from such infections to in-contact birds, both unvaccinated unchallenged, or already infected with one of the viruses. This can help us understand how the viruses may interact in nature and whether one virus would eventually disappear over time as it was outcompeted by the other.
3. The objective above could also be met to some extent by surveying commercial chickens not vaccinated with Rispens/CVI988 for the presence of the virus, particularly unvaccinated broiler chickens in reasonable proximity to layer or breeder farms where Rispens/CVI988 is used.
4. It would also be worthwhile to determine the extent to which mixed infections of MDV and Rispens/CVI988 occur in the field. Walkden-Brown *et al.* (2013a) reported that in dust samples collected from broiler flocks, vaccination with HVT reduced qPCR detection of MDV-1 from 26.1 to 16.4% of samples.
5. There are no reports of pathotyping experiments in which the effects of vaccination with HVT, bivalent (HVT + MDV-2) and Rispens/CVI988 vaccines have been directly compared in the same experiment. Such experiments would improve our understanding of the relative protective effects of the different vaccines.
6. In an experiment such as that above, inclusion of a trivalent HVT + MDV-2 + Rispens/CVI988 treatment and measurement of viral kinetics would provide useful

information on how all of the vaccinal viruses compete with pathogenic MDV in a single host.

7. Viral kinetic studies in experiments involving challenge of Rispens/CVI988-vaccinated and unvaccinated chickens with MDV strains of divergent virulence would provide a further test of vaccinal selection for MDV strains of higher virulence.
8. Our experiments of necessity were limited in time to 56 dpc. Ideally kinetic studies in the field would shed light on the persistence of Rispens/CVI988 virus and its shedding rate over the lifespan of layer and breeder chickens. Long-term co-infection studies would also provide useful information on the competition between viruses in the same host over a longer period.

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