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EQUINE

Virus-neutralising antibody responses in horses following vaccination with Equivac® HeV: a field study

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Objective To determine the antibody responses to a commercial Hendra virus vaccine (Equivac® HeV) in a field environment.

Methods A group of 61 horses received a primary vaccination course comprising two doses administered 3–6 weeks apart (V1, V2) and a 3rd dose (V3) given 6 months after the second. This was followed by booster vaccinations at 12 monthly intervals (V4, V5). Antibody titres were assessed using a virus-neutralisation test.

Results Neutralising antibodies against HeV were not detected prior to vaccination. Antibodies were detected in 54/57 horses at 3 weeks after V1 and 51/51 had titres ≥ 32 at 8 weeks after V2. At 6 months after V2, antibody titres decreased in most (31/34) horses and were not detected in three horses. A rapid increase in antibody titres was recorded in 35/36 horses at 1 week following V3. By the first annual booster vaccination (V4), antibodies were still detectable in 29/29 horses, although titres had decreased; in 26/29 horses, titres remained ≥ 32. All horses showed an increase in antibody titres after V4. There was no statistically significant increase in mean antibody titre after V5, compared with after V4.

Conclusion Horses administered Equivac® HeV, using a primary vaccination course followed by annual booster vaccinations, mounted an effective secondary immune response and acquired antibody responses that were consistent with protective immunity against HeV in the form of virus-neutralising antibodies. No adverse events were observed after vaccine administration.

Keywords Hendra virus; horses; vaccination; vaccine efficacy; virus-neutralising antibody titres

Abbreviations APVMA, Australian Pesticides and Veterinary Medicines Authority; CI, confidence interval; HeV, Hendra virus; HeVsG, Hendra virus soluble G; SNT, serum-neutralising antibody titres; V1, 1st vaccination; V2, 2nd vaccination; V3, 3rd vaccination; V4, 4th vaccination; V5, 5th vaccination

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A commercial Hendra virus (HeV) vaccine for horses (Equivac® HeV Hendra Virus Vaccine for Horses, Zoetis Australia Pty Ltd) became available in November 2012. The vaccine contains a soluble HeV G (HeVsG) glycoprotein antigen and antibodies against this protein can neutralise HeV.[1] In a vaccine efficacy study, all of seven horses given two intramuscular doses of the vaccine 3 weeks apart were protected from infection after oronasal exposure to an otherwise lethal dose of a low-passage HeV isolate.[2] Similar observations were made in two of three horses exposed to HeV 6 months after vaccination: the third horse remained clinically healthy and evidence of HeV replication was limited to detection of transient low-level viral genome (but not virus) in nasal secretions.[2]

The vaccine efficacy study used a HeV challenge dose that reliably induced lethal infection.[2] Under laboratory conditions, the horses with serum-neutralising antibody titres (SNT) as low as 16 were protected from infection.[2] It is possible that protection from field exposure to virus may also occur in immunised horses with lower (or even undetectable) titres. The reasons for this include the rapid time-frame over which extensive mucosal exposure to infective fluid occurs under experimental conditions and the fact that protection will depend upon the development of an anamnestic response, in addition to pre-existing antibody levels.

Prior to May 2016, the product label of Equivac® HeV, approved by the Australian Pesticides and Veterinary Medicines Authority (APVMA approval no. 68996), required that horses be vaccinated under a regimen of two doses at an interval of 3–6 weeks followed by booster vaccinations at 6-monthly intervals. The objective of the current study was to monitor HeV neutralising antibody responses in horses receiving annual (12-monthly) boosters following a primary vaccination course comprising two doses administered 3–6 weeks apart and a 3rd dose given 6 months after the 2nd dose. The data generated from this study were submitted to APVMA in support of an application for approval of a regimen of annual boosters after the primary vaccination course.

Materials and methods

Horses

The 61 horses comprising the institutional herd of the College of Public Health, Medical & Veterinary Sciences Veterinary College for James Cook University were enrolled in the study. Ethics approval was obtained from the James Cook University Animal Ethics Committee (approval no. A1876). There were 49 Thoroughbreds, 4 Quarter Horses, 5 Standardbreds and 3 Australian Stock Horses, including 1 stallion, 8 geldings and 52 mares. The mean age was 13.6 years with a minimum of 2 years and a maximum of 28 years. Clinical examinations were undertaken on each horse at each vaccination and sampling time.

Under normal herd management practices, horses entered and exited the herd as the study progressed. As a result, not all horses completed the full vaccination regimen.

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Vaccination protocol

Equivac® HeV was used in the study. The 1 mL vaccine contains not less than 100 µg of HeVsG glycoprotein antigen adjuvanted with 250 µg/dose of immuno-stimulating complex. Each 1 mL dose was administered by intramuscular injection into the left side of the neck. After the first vaccination (V1), a second dose (V2) was administered 3–6 weeks later, followed by a third dose (V3) 6 months later. Vaccinations V1–V3 were considered the primary vaccination course, after which annual boosters were administered. Depending on when the horse entered the institutional herd, either one (V4, first annual booster) or two (V5, second annual booster) annual vaccinations were administered during the study (Table 1). Based on the precise timing of vaccinations and blood sample collections, the time points defined for subsequent analysis of antibody titres are outlined in Figure 1.

Sample collection and storage

Blood samples were collected from horses immediately prior to each vaccination and at intervals afterwards (Table 1). A total of 8 mL of blood was collected from each horse via jugular venepuncture into plain blood tubes using a Vacutainer® and an 18-gauge needle. Blood samples were left to stand for 30 min at room temperature to allow satisfactory clotting. The blood samples were then centrifuged at 1200*g* for 7 min. The serum was decanted into paired screw-capped serum tubes labelled with an identical sample identification number. Sera were chilled to 2–8°C, then frozen at −40°C until shipped on dry ice for analysis.

Sample analysis

Detection of antibodies to HeV by SNT was performed within the Biosecurity Level 4 facility at the CSIRO Australian Animal Health Laboratory, Geelong, Victoria, as previously described.[3] Titres were expressed as the reciprocal of the serum dilution. For this study, the upper limit of the neutralisation assay was 8192. Accordingly, any sample with a titre >8192 was assigned the value of 8192 for further data analysis. Similarly, any sample with a titre below the limit of detection (SNT < 8) was assigned the value of 4 for further data analysis.

Statistical analysis

When evaluating the rise and fall of antibody titres within individual horses, an increase or decrease in titre was considered to have occurred when there was a difference of more than two doubling dilutions between the two test results.

Serum antibody titres for the study cohort were log-transformed (natural logarithm, base e) and analysed using a general linear mixed model for repeated measures, with terms including the fixed effects of 'time point', plus random effects including 'animal'. Geometric means and 95% confidence intervals (CIs) were calculated at each time point following back-transformation, along with minimum and maximum titres. Time points where all titres were below the limit of detection were omitted from the analysis. Geometric mean titres just prior to each vaccination (V2–5) were also compared between consecutive vaccinations, using contrast statements involving the geometric means at

Table 1. Vaccination against Hendra virus (HeV) and blood sampling regimen for the detection of HeV antibodies by SNT in 61 horses

Week	Vaccination and sampling points	Time samples taken	Mean study day (min–max)	No. of horses	SNT range (min–max)
0	V1	on or prior to the day of V1 (day 0)	-1 (-9–0)	56	< 8–< 8*
3	V2	on the day of V2 (days 19–30)	21.4 (19–30)	57	< 8–4096
11	V2 + 8 weeks	8 weeks (± 2 weeks) after V2	73.5 (68–91)	51	32–2048
19	V2 + 16 weeks	16 weeks (± 2 weeks) after V2	129 (119–149)	51	< 8–512
29	V3	26 weeks (± 2 weeks) after V2, prior to V3	202.7 (195–205)	38	< 8–256
30	V3 + 1 week	7 days (± 2 days) after V3	209.5 (202–211)	37	32–8192
38	V3 + 9 weeks	9 weeks (± 2 weeks) after V3	264.9 (256–281)	35	32–4096
46	V3 + 17 weeks	17 weeks (± 2 weeks) after V3	321.3 (304–338)	32	16–4096
54	V3 + 25 weeks	25 weeks (± 2 weeks) after V3	377.4 (370–378)	30	16–2048
64	V3 + 35 weeks	35 weeks (± 2 weeks) after third vaccination	444.6 (439–454)	31	16–4096
73	V3 + 44 weeks	44 weeks (± 2 weeks) after V3	510.4 (503–511)	29	8–2048
83	V4	54 weeks (± 2 weeks) after V3, prior to V4	581.4 (574–582)	29	8–1024
89	V4 + 6 weeks	6 weeks (± 2 weeks) after V4	621.4 (614–622)	29	64–8192
95	V4 + 12 weeks	12 weeks (± 2 weeks) after V4	665.4 (658–666)	29	16–8192
105	V4 + 22 weeks	22 weeks (± 2 weeks) after V4	735.4 (728–736)	29	16–8192
113	V4 + 30 weeks	30 weeks (± 2 weeks) after V4	791.4 (784–792)	27	16–8192
134	V5	51 weeks (± 2 weeks) after V4, prior to V5	935.3 (928–936)	26	8–8192
138	V5 + 4 weeks	4 weeks (± 2 weeks) after V5	964.3 (957–965)	26	128–8192

*< 8 is the SNT limit of detection.
HeV, Hendra virus; SNT, serum-neutralising antibody titres; V1, 1st vaccination; V2, 2nd vaccination; V3, 3rd vaccination; V4, 4th vaccination; V5, 5th vaccination.

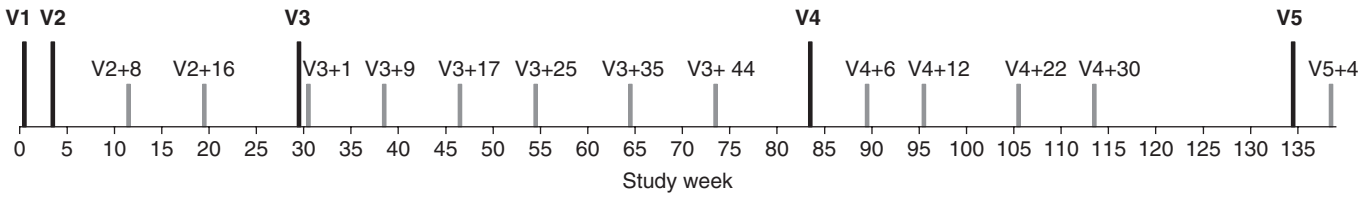

Figure 1. **Timeline for Hendra virus vaccination and sampling. Major lines represent vaccinations (V1–5), and smaller lines represent blood sampling times.**

the relevant time points. Similarly, geometric means at 4–9 weeks' post-vaccination (V2–5) were also compared between consecutive vaccinations, using contrast statements. Additional contrast statements were used for other comparisons of interest.

Results

Horses

No local or systemic reactions attributable to vaccination were observed during this study and no adverse events following immunisation were recorded.

Vaccination and sample collection

The number of horses and timing of sampling are recorded in Table 1. The number of animals vaccinated and sampled at each time point differed as horses entered and exited the herd over time according to management practices. This meant that on any given sample date, individual horses may have been at dissimilar stages of the vaccination protocol. All 57 horses received V1 and 57 horses had V2, although one horse was acquired after V1 had been administered and sampling was commenced at the time of V2. In total, 38 horses received V3, 29 horses had V4 and 26 horses remained within the herd for the entirety of the study to receive V5.

SNT to HeV

Neutralising antibodies against HeV were not detected in any horse prior to vaccination.

The timing of SNT peaks post-vaccination could not be established with confidence because sampling times differed after each vaccination and not every horse received all immunisations (Table 1). Accordingly, the mean SNT recorded 4–9 weeks post-vaccination was used for comparative analysis between time points because the highest mean SNT was recorded in that time, except for V3 + 1wk, and data were consistently available for those periods (Figure 2). The mean SNT result at V3 + 9 weeks was 466.5 (95% CI, 299.8–725.8). The highest observed mean antibody titre following V3 (V3 + 9 weeks) was significantly higher than that collected at an equivalent time following V2 (V2 + 8 weeks, $P = 0.0455$), and significantly higher mean titres were observed after V4 (V4 + 6 weeks) compared with V3 (V3 + 9 weeks, $P < 0.0001$). The highest titres post-V4 (V4 + 6 weeks) were also significantly higher than those recorded after V5 (V5 + 4 weeks, $P = 0.0007$). Pre-vaccination titres rose significantly with successive V3, V4 and V5 vaccinations ($P < 0.0001$).

In individual horses, antibodies were detected in 54/57 horses at 3 weeks after V1, and 51/51 horses had titres ≥ 32 when assessed 8 weeks after V2, including three horses in which antibodies were not detected after V1 (Figure 3). A significant rise in mean antibody titre was observed at, and following, V2 ($P < 0.0001$). At 6 months after V2, antibody titres had decreased in most horses (31/34) and

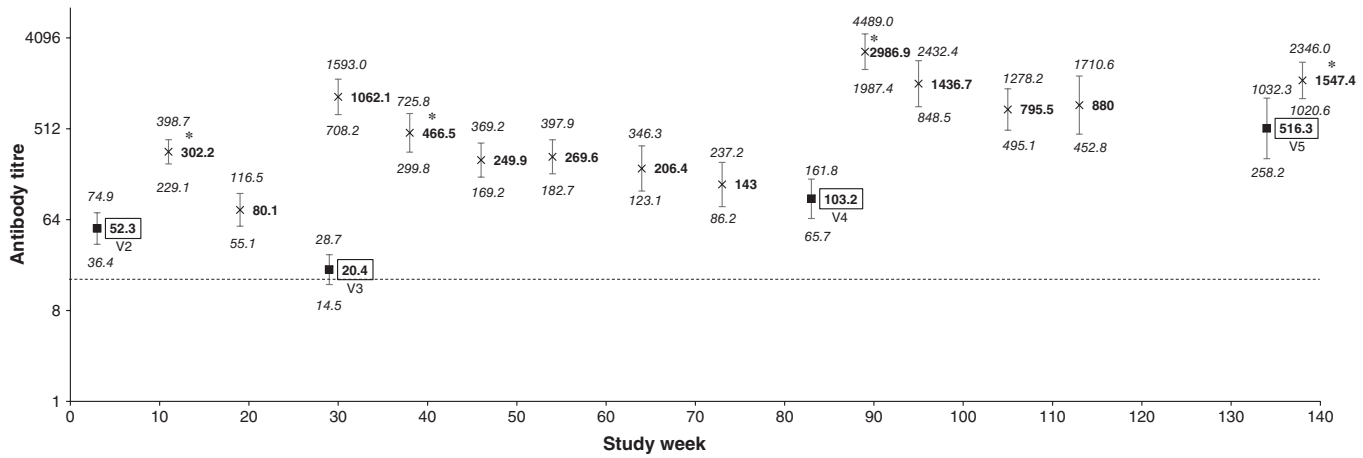

Figure 2. **Hendra virus serum-neutralising antibody titres (SNT) at each sampling point with geometric means in bold and 95% confidence interval in italics (log_2 scale Y-axis: black squares with bordered means and text below indicate vaccination time points; crosses represent blood sampling only times; dotted line represent previously reported minimum protective SNT of 16; *peak SNT comparatively analysed 4–9 weeks post-vaccination.**

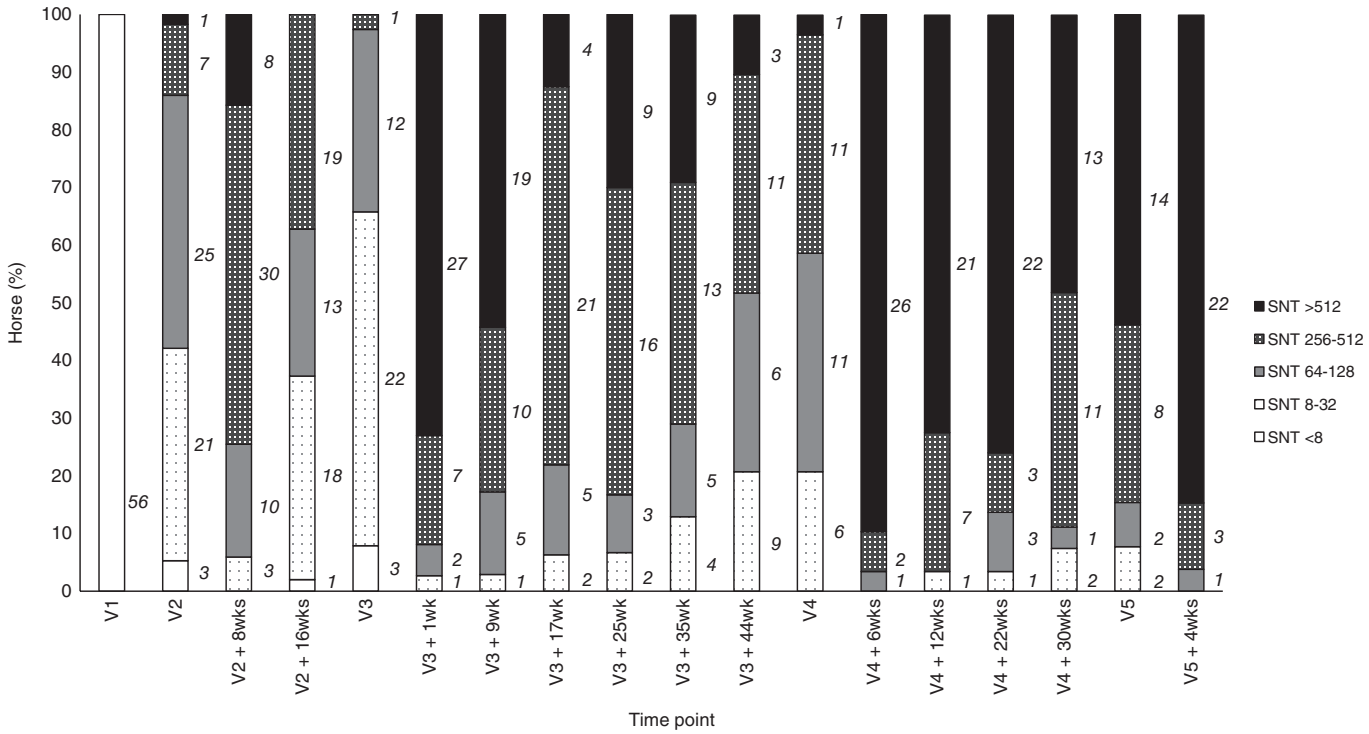

Figure 3. Proportion of horses grouped by Hendra virus serum-neutralising antibody titres (SNT) at each sampling time, with the number of horses indicated in italics to the right of each column.

were not detected in three animals. However, titres remained ≥ 16 in 29 horses. Importantly, a rapid increase and significantly higher titres were recorded in 35/36 horses 1 week following V3 (P = 0.0045), with a further horse showing a rise in titre from 8 to 32. Longitudinal data from another animal suggested it had not been exposed to vaccine antigen at the V3 time point, most likely caused by a V3 handling or administration error. On that basis, data from this horse were excluded from any analysis after the V3 sampling period.

Prior to V4, antibodies were still detectable in 29/29 horses, although titres had decreased in 21 animals; in 26/29 horses, titres remained ≥ 32. All horses showed a boost in antibody titres after V4, consistent with reactivation of a secondary immune response. Importantly, significantly higher antibody titres were recorded in response to V4, compared with the titres recorded following either V2 or V3 (P < 0.0001). At V5, titres in 25/26 horses were ≥ 32, although titres had decreased in 12 animals. Interestingly, a rise in titre at 4 weeks after V5 was recorded in only 5/26 horses, while titres of virus-neutralising antibody were unchanged in the remaining 21 animals. Statistically, there was no significant rise in mean antibody titre in response to V5 compared with after V4. In fact, a slightly lower mean titre was recorded (P = 0.0007). Lastly, mean antibody titres following both V4 and V5 were significantly higher than those following V3 (P < 0.0001).

Discussion

This study showed that a diverse cohort of horses reliably developed detectable neutralising-antibody responses to HeV, consistent with recognition by the equine immune system of neutralising epitopes on the recombinant HeVsG glycoprotein antigen incorporated into the vaccine formulation.[4] Although the principle of vaccination is to establish a 'primed' state that will lead to an effective secondary immune response on exposure to field virus, preformed antibody also plays a role in protective immunity. Correlates of protection in the form of preformed antibody titres are generally difficult to establish, especially where the natural infection is sporadic and, for Biosafety Level 4 pathogens such as HeV, where experimental animal studies are costly and difficult to perform. Currently, the most useful data derive from henipavirus vaccine efficacy studies using live virus, where preformed neutralising antibodies against the G glycoprotein of the virus reliably afford protection for animals against clinical disease: titres at the time of virus exposure have been as low as 16 in ferrets or 16–32 in horses.[2,5] In the current study, all horses achieved an antibody titre of at least 32 following V2, V3, V4 and V5. Although detectable neutralising antibody lasted for varying periods of time in individual horses, titres of at least 16 persisted in most animals up to the first 6-monthly booster and were maintained in all but one horse up to subsequent booster vaccinations.

The magnitude of the antibody response to V2 was consistent with activation of a secondary immune response, reflecting effective establishment of immunological memory by the initial priming dose of vaccine (V1). In these vaccinated horses, exposure to infectious virus should be followed by early and vigorous production of high-affinity antibody, and thus reduced risk of infection and disease. Although the role of affinity in determining the neutralising potency of antibodies is poorly understood, it is possible that the increasing

antibody titres observed with successive immunisations also reflected increased neutralisation potency attributable to affinity maturation.[6,7]

Similarly, the magnitude and rapidity of the antibody response 6 months later, 1 week after V3, was consistent with reactivation of immunological memory. Further expansion of the memory clone also occurred following V3, as evidenced by continuing augmentation of antibody titres following exposure 12 months later to V4, thus emphasising the critical role of the first 6-month booster within the primary vaccination course to establish a key element of protective immunity.

Importantly, in the context of protective immunity against HeV, extension of the booster interval to 12 months after the primary vaccination course (V1–3) did not compromise either reactivation of immunological memory or the magnitude of the antibody response on re-exposure to antigen. The stability of antibody titres in most horses post-V5 suggested that, at the time of V5 vaccination, antibody and memory T cells remaining in the immunised horse prevented activation of naive B and T cells.[8] Similar observations have been made in both HeV and Nipah vaccine efficacy studies in horses, non-human primates, ferrets and cats, in which animals also had detectable preformed vaccine-induced antibodies in serum.[2,3,5,9,10] This observation raises the possibility that extension of booster intervals beyond 12 months after V4 may be possible. The objective of a 'booster' after a primary vaccination series is to provide rapid protective immunity against infection. The determination of booster schedules in immunologically competent individuals is most commonly measured using four methods: the anamnestic response after administration of a booster dose, the infection rate in vaccinated populations, in vitro B- and T-cell activity testing, and seroepidemiological studies.[11] Any extension of booster intervals beyond the current 12-month interval would need to be based on additional evidence of persistence of immunological memory to Equivac® HeV in a larger horse population. However, this possibility needs to be balanced by the observation that one horse in our cohort had a titre of only 8 prior to the administration of V5, and so there is the possibility that more frequent booster doses may be required for immunocompromised patients, based on serological monitoring.

The most common clinical sign associated with Equivac® HeV reported by the Adverse Experience Program of the APVMA to 20 September 2016 was injection site reactions.[12] The reaction incidence percentage for site reactions was reported at 0.2%, whereby the percentage is calculated as the total number of animals in which a presenting sign has been classified as probably or possibly linked to the administration of the Hendra vaccine/number of doses sold multiplied by 100.[12] As minor adverse events may not have been reported by owners, this may be an underestimate of adverse reactions. In consideration of this, 206 doses of the vaccine were administered during this study. With an incidence percentage of 0.2%, less than one adverse experience would have been expected to occur. Despite some horses recording high SNT at the time of the vaccination, no adverse reactions were noted during the study, suggesting that they may not be associated with circulating antibody titres but with inherent individual horse factors. The lack of recorded adverse events appears to be within the APVMA reaction incidence percentage. In comparison, injection site reactions were also the most commonly reported adverse experience noted in Australian horses administered the equine influenza vaccine during the 2007 outbreak, but anecdotally reported at a significantly higher rate – up to 25% of vaccinated horses.[13] Similarly in human medicine, injection site pain is the most common side effect of influenza vaccines and reported to occur in up to 52.9% of vaccine recipients.[14]

This study confirmed that horses administered Equivac® HeV using a primary vaccination course followed by annual booster vaccinations mounted an effective secondary immune response and acquired protective immunity in the form of virus-neutralising antibodies.

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Conflicts of interest and sources of funding

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A Hodge, N Edwards and JA Huang were employees of Zoetis at the time of the study. The remaining authors declare no conflicts of interest for the work presented here.

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OBITUARY

Sydney John Miller

1926–2017

Sydney John Miller was born in Tambo, Queensland and attended boarding school as a boy. On being granted a scholarship from the Department of Primary Industries (DPI), Syd started his degree in Veterinary Science at the University of Queensland, but unfortunately this was abandoned during the war. Syd completed his degree at the University of Sydney in 1949, and in the same year became a member of the Australian Veterinary Association (AVA). Bureaucratic infighting denied Syd the opportunity to attend to the graduation ceremony of either University. This wrong was righted many years later when he attended a graduating ceremony at the University of Queensland.

After graduation, Syd spent five years working for the DPI in the Sheep and Wool branch to fulfil his scholarship obligations. During this time, he rose to the position of Assistant Director.

Following his stint in the DPI he managed Buckinbah Merino Stud in south-west Queensland for four years (1954–1957). At that time Buckinbah sold 1500 rams annually and ran 2000 cows.

In 1958 he entered private practice in Warwick, where he stayed until 1982. During this time, between the routine mixed practice work, Syd developed a major sheep AI business, inseminating more than 500,000 ewes. He also worked as a private veterinary consultant for many of Australia's leading stud and commercial operations and with GRM on overseas projects. This work saw him involved in some 27 different projects in 17 developing countries.

In the late 1970s, encouraged by his close friend and client Mr Don Anderson of Inverary Polled Herefords, he developed an interest in the emerging technology of bovine embryo transfer. He retired from regular practice in 1982 to focus on embryo transfer full-time, before retiring in 2000.

His service to the veterinary profession saw him take on roles in numerous committees and subcommittees of the AVA (1967–1973) and the Australian College of Veterinary Scientists (1972–1980). He was a member of the Queensland Veterinary Surgeons Board (1974–1984), President of the Queensland division of the AVA in 1970 and President of the Australian College of Veterinary Science in 1976. All these achievements were recognised in 1986 when he was awarded an OBE for his service to the Australian Pastoral Industry and Developing Countries in the field of Veterinary Science.

Besides his academic qualifications, BVSc (1949), MVSc (1957), and FACVSc (1974), Syd was awarded the AVA Gilruth prize (1976) for meritorious service to the veterinary profession in Australia, made a Fellow of the Australian Society of Animal Production (1982), awarded the AVA Kestivan medal (1983) for his contribution to veterinary science in developing countries and was made an AVA Lifetime Member in 1992.

Syd's immense knowledge of all aspects of the pastoral industries combined with his acute intellect and boundless energy meant he was recognised worldwide as an expert in sheep management, genetics and artificial reproduction.

He had an illustrious career in veterinary science and contributed greatly to the profession and to the careers of the many veterinarians who were privileged to work with him. His guidance and advice were also instrumental in cementing many primary producers as leaders in their chosen areas.

Syd was the greatest of mentors, the finest of colleagues and a most loyal friend.

His no-nonsense clarity of thought, his strict application of science to all veterinary procedures and his abhorrence of process over results made him a giant in the veterinary profession. His total devotion to his family made him a giant of a man.

He leaves behind his wife of 66 years Heather, four daughters, Deborah, Lucille, Jane and Melissa, five grandchildren and three great grandchildren. We extend our sincere sympathy to his family and can assure them he will not be forgotten by any who knew him.

C Wise

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