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Adverse reactions in cattle after vaccination with lapinized rinderpest virus

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INTRODUCTION

The endemicity of rinderpest in Kenya was broken by 1947 through the widespread and compulsory use of attenuated goat virus vaccine in native areas during the preceding seven years (Daubney, 1949*a*). Vaccinations are still maintained because of the threat of the reintroduction of the disease by trade cattle and wild game from Ethiopia and Somalia.

In cattle attenuated goat virus induces a well-defined thermal and clinical response which is mild in indigenous stock but can be severe in exotic animals. Consequently considerable interest was aroused by the paper on the more attenuated lapinized rinderpest virus presented by Cheng and Fischman to the 1948 Rinderpest Conference in Nairobi. Ampoules of the Nakamura III strain of lapinized rinderpest virus were obtained, from which Brotherston (1951*a*, *b*) developed the freeze-dried lapinized rinderpest virus vaccine now used in East Africa. The first batches of vaccine were issued in 1949 and its popularity in Kenya can best be judged by the steady increase in annual issues. Only the Sanga type of cattle of Ankole exhibited a clinical reaction after vaccination. Other breeds in East Africa, including purebred European cattle, were successfully immunized without incident (Brotherston, 1951*b*). The vaccine was regarded by field officers as being 'safe'. However, in 1954, 47 previously unvaccinated young Guernsey cattle in one herd developed alarming post-vaccinal reactions. The incident was reported by Brown, Scott & Brotherston (1955), who suggested that the important factor was the low innate resistance of the cattle and not the virulence of the virus. Thereafter an attempt was made to trace the effect in cattle of every dose of lapinized rinderpest virus used in Kenya during the next 30 months. The findings are herein recorded.

MATERIALS AND METHODS

Survey

The expected response of Kenya cattle given lapinized rinderpest virus is an inapparent infection. A reactor was therefore defined as any animal which deviated from normal health following vaccination. Field officers of the Department of Veterinary Services were contacted and asked to supply the following data: the numbers and types of cattle vaccinated, the batch number of the vaccine used,

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the numbers and types of cattle which reacted after vaccination, the rinderpest immunity status of the reacting cattle before vaccination, the ages of the reacting cattle, the blood relationships of reacting cattle within a herd, the lengths of the incubation periods, the lengths of the clinical periods, descriptions of the clinical signs, and the presence or absence of complicating factors such as other vaccinations or intercurrent diseases. In addition, field officers were instructed that all reports of reactions were to be investigated immediately. If the reactions simulated rinderpest the field officer was requested to contact the Veterinary Laboratory, Kabete, either by telephone or telegram. The author visited the farm if there was any hope of isolating virus.

Retests of vaccine batches

Whenever adverse reactions were reported the production protocols of the incriminated batch of vaccine were examined. Sample ampoules of each batch are always held in the laboratory and in the earlier months of the investigation these ampoules were retested in rabbits and cattle.

Virus isolations

Experience revealed that recovery of virus from suspect blood samples was only successful if the samples were fresh and in later investigations rabbits were taken to the farm and inoculated intravenously on the spot. The tissues of rabbits which reacted were harvested and emulsified. Part of the emulsion was freeze-dried and stored and part was inoculated subcutaneously into Kenya grade cattle whose subsequent response was carefully recorded. Inoculated cattle were housed with an equal number of susceptible cattle.

RESULTS

Incidence of adverse reactions

Between 1 January 1954 and 30 June 1956, 310,971 cattle were vaccinated with lapinized rinderpest vaccine in Kenya. Post-vaccinal reactions occurred in 278 cattle, giving an incidence rate of 0·09 %. Twenty deaths attributable to vaccinations occurred, giving a post-vaccinal mortality rate of 0·006 % and a case mortality rate of 7·2 %. Four types of reactions were observed. In descending order of incidence they were 'rinderpest-like' reactions, aggravations of latent protozoal infections, transient spermatolysis and anaphylaxis (Table 1). In addition, blackquarter occurred in 9 cattle on two adjacent farms after vaccination. A case of heartwater which terminated fatally 7 days after vaccination may have been an aggravation of a latent infection or a chance simultaneous development of acute heartwater.

Genuine rinderpest-like reactions affected 217 cattle, giving an incidence rate of 0·07 %. The mean incubation period was 6·9 days with 95 % fiducial limits of ± 1·7 days. The clinical signs were characteristic of rinderpest and varied from transient thermal reactions together with slight lachrymation and slight diarrhoea to severe reactions with temperatures up to 107° F., marked foetid diarrhoea and

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erosions of the oral mucosa. The most common sequel was a marked loss in condition which lasted for several weeks. The next commonest sequel was abortion. One hundred and twenty-one of the 217 reactors were pregnant and 72 aborted, giving a case abortion rate of 60 %. However, 61 of the abortions occurred in one herd, which was later shown to be riddled with venereal and genital diseases. Elsewhere the case abortion rate was 18 %. Deaths were rare and only one genuine rinderpest-like death was observed, giving a case mortality rate of 0·5 %. The over-all post-vaccinal mortality rate associated with rinderpest-like reactions was 0·0003 %. A characteristic of the incidence of rinderpest-like reactions was the tendency for several animals to be affected in the same herd. The mean percentage of the number of cattle which reacted within reacting herds was $17 \cdot 0 \pm 8 \cdot 1$.

Table 1. *Incidence of adverse reactions in Kenya cattle after vaccination with lapinized rinderpest virus*

Year	Cattle vaccinated	Rinderpest-like reactions	Aggravations of protozoal infections	Transient spermatolysis	Anaphylaxis	Total
1954	110,645	99	16	—	1	116
1955	100,612	61	8	6	—	75
1956	99,714	57	28	—	2	87
Total	310,971	217	52	6	3	278

Aggravations of latent diseases were observed in 52 animals. The case distribution was sporadic. Nineteen deaths occurred, giving a case mortality rate of 36·5 %. Protozoal infections implicated were anaplasmosis, babesiasis and theileriasis.

Transient spermatolysis developed in six vaccinated Red Poll bulls on one farm. The standard of bull management was excellent and daily records were kept of each bull's temperature. After vaccination none of the bulls exhibited a thermal or clinical reaction. However, semen samples taken on the 5th through to the 14th day after vaccination were abnormal and the spermatozoa were non-motile. Thereafter the motility returned.

Anaphylactic shock occurred immediately after vaccination in three animals. Two were Sahiwal-zebu crossbreds. The third was a low grade Aberdeen-Angus steer.

Incidence within species

Data are recorded in Table 2. The vaccinated cattle were *Bos indicus* and *Bos taurus* and the majority were crosses between the species. The incidence of rinderpest-like reactions was highest in high grade *Bos taurus–Bos indicus* crosses (Table 3). The difference between the incidence rates in high-grade *Bos taurus–Bos indicus* crosses and *Bos taurus* was not however significant ($\chi^2 = 1178$, $P > 0 \cdot 20$) whereas the difference in incidence between high and low grade cattle was significant ($\chi^2 = 75 \cdot 504$, $P < 0 \cdot 001$). Rinderpest-like reactions did not occur in 87,787 vaccinated *Bos indicus*.

Aggravations of latent protozoal infections were not observed in *Bos indicus*.

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The incidence of aggravated latent infections was highest in *Bos taurus* (Table 3). The incidence rates in high and low grade *Bos taurus–Bos indicus* crosses were similar ($\chi^2 = 0{\cdot}316$, $P > 0{\cdot}50$) and were significantly lower than in *Bos taurus* ($\chi^2 = 61{\cdot}757$, $P < 0{\cdot}001$). A re-investigation revealed that only pedigree imported *Bos taurus* cattle were involved and that they had all been inoculated with *Babesia* and *Anaplasma* prior to rinderpest vaccination. None of the pedigree cattle died. Fifteen (58 %) of the high grade *Bos taurus–Bos indicus* reactors died. Four (29 %) of the low grade *Bos taurus–Bos indicus* reactors died.

The transient spermatolysis was noted in *Bos taurus* bulls. The anaphylactic reactions occurred in two *Bos indicus* and in a low grade *Bos taurus–Bos indicus* cross.

Table 2. *Species incidence of adverse reactions in cattle after vaccination with lapinized rinderpest virus*

		Number of reactors			
Species	Number of cattle vaccinated	Rinderpest-like reactions	Aggravations of latent disease	Transient spermatolysis	Anaphylaxis
Bos indicus	87,787	0	0	0	2
Bos taurus	4,043	6	12	6	0
Bos taurus × *Bos indicus*					
High grade	75,784	188	26	0	0
Low grade	51,828	23	14	0	1
Unclassified	91,529	0	0	0	0

Table 3. *Incidence rates of adverse reactions in different species of cattle vaccinated with lapinized rinderpest virus*

	Percentage incidence	
Species	Rinderpest-like reactions	Aggravations of latent disease
Bos indicus	0	0
Bos taurus	0·15	0·30
Bos taurus × *Bos indicus*		
High grade	0·25	0·03
Low grade	0·04	0·03

Incidence within breeds

Data are recorded in Table 4. Insufficient numbers of cattle of the Galloway, South Devon, Sussex and Swiss Brown breeds were vaccinated for valid conclusions to be drawn regarding the true incidence of post-vaccinal reactions in these breeds.

Rinderpest-like reactions were observed in four breeds of cattle—Ayrshire, Guernsey, Jersey and Red Poll (Table 5). The incidence in Guernsey cattle was

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significantly greater than in the other three breeds ($\chi^2 = 34{\cdot}418$, $P < 0{\cdot}001$). The animal which died was a Guernsey.

The ratio between herds with and without reactors gives a more realistic picture of the incidence of rinderpest-like reactions. Reactors occurred in 2 out of 177 Ayrshire herds (1 %), in 6 out of 151 Guernsey herds (4 %), in 2 out of 75 Jersey herds (3 %) and in 2 out of 63 Red Poll herds (3 %). Two of the 6 reacting Guernsey herds accounted for 47 and 61 reactors respectively or, in other words, 75 % of the Guernsey cattle that reacted.

Table 4. *The breed incidence of adverse reactions in cattle after vaccination with lapinized rinderpest virus*

		Number of reactors			
Breed	No. of cattle vaccinated	Rinderpest-like reactions	Aggravations of protozoal infections	Transient sperma-tolysis	Anaphy-laxis
Aberdeen Angus	787	0	0	0	1
Ayrshire	40,302	20	24	0	0
Friesian	30,444	0	10	0	0
Galloway	81	0	0	0	0
Guernsey	26,837	144	11	0	0
Hereford	2,923	0	3	0	0
Jersey	9,796	21	3	0	0
Red Poll	15,020	32	1	6	0
Sahiwal	2,332	0	0	0	2
Shorthorn	5,193	0	0	0	0
South Devon	62	0	0	0	0
Sussex	24	0	0	0	0
Swiss Brown	186	0	0	0	0
Zebu	85,455	0	0	0	0
Unclassified	91,529	0	0	0	0

Table 5. *Incidence rates of adverse reactions in different breeds of cattle vaccinated with lapinized rinderpest virus*

	Percentage incidence	
Breed	Rinderpest-like reactions	Aggravations of latent disease
Ayrshire	0·05	0·06
Friesian	0	0·03
Guernsey	0·54	0·04
Hereford	0	0·10
Jersey	0·21	0·03
Red Poll	0·21	0·01

Aggravation of latent protozoal infections occurred in Ayrshire, Friesian, Guernsey, Hereford, Jersey and Red Poll cattle. The incidence was highest in Hereford cattle and lowest in Red Polls but the difference cannot be tested for significance because of the small numbers of cattle involved within each breed (Table 5). Fourteen (58 %) of the Ayrshire reactors, 5 (45 %) of the Guernsey reactors and the only Red Poll reactor died. The Friesian, Hereford and Jersey reactors survived.

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The transient spermatolysis occurred in Red Poll bulls. The anaphylactic reactions appeared in Aberdeen-Angus and Sahiwal cattle.

Familial incidence

The incidence of rinderpest-like reactions within reacting herds was $17{\cdot}0 \pm 8{\cdot}1\%$. The rinderpest-like reactors within a herd were always related, usually through the sire. Amongst Guernsey cattle, nearly 80% of the rinderpest-like reactors occurred in one blood line.

Significant blood relationships were not detected in cattle with aggravated protozoal infections, nor in the bulls with transient spermatolysis.

Two of the cattle which exhibited anaphylaxis were related, the one being the dam of the other. The younger was only two weeks old and its response was considered to be due to passively transferred sensitization.

Sex incidence

Six of the 217 rinderpest-like reactors were bulls, giving a ratio of 1/36. The Kenya Agricultural Census, 1954, recorded a sex ratio of 1/33 (Anon, 1955). Sex therefore probably did not influence the incidence. Likewise sex did not influence the incidence of aggravated latent infections. A 'flare-up' was observed in one vaccinated bull. The remainder occurred in female stock. Two of the 3 cattle which developed anaphylaxis were females.

Age incidence

Ninety-nine of the rinderpest-like reactors were less than 18 months of age and 118 were older. The ratio was similar to that noted in the Kenya Agricultural Census, 1954 (Anon, 1955). In other words, differences in innate resistance due to age were not evident. Similarly, age did not influence the incidence of aggravated latent infections. The cattle exhibiting anaphylaxis were 2 weeks, 3 years and 10 years old, respectively.

Immunological status of reactors

Rinderpest-like reactions occurred only in previously unvaccinated cattle. In Kenya outbreaks of rinderpest are now infrequent. Nevertheless, most cattle are immune through vaccination and only one-third of the animals presented for vaccination are estimated to be previously unvaccinated. If these are the cattle at risk, the percentage incidence rates of rinderpest-like reactors in Ayrshire, Guernsey, Jersey and Red Poll cattle are increased to 0·15, 1·61, 0·64 and 0·64, respectively (Table 6).

Fifty-one of the cattle in which lapinized rinderpest virus aggravated latent infections were previously unvaccinated. The remaining animal was an adult high grade Guernsey which had been vaccinated with lapinized rinderpest virus $2\frac{1}{2}$ years before and was therefore probably susceptible when revaccinated. If susceptible cattle are the true cattle at risk, the incidence rates of aggravated latent infection are increased to a high of 0·3% in Herefords and to a low of 0·02% in Red Polls (Table 6).

The transient spermatolysis occurred in rinderpest-susceptible bulls.

Two of the cattle exhibiting anaphylaxis were vaccinated for the first time. The third animal had been vaccinated annually for several years and during the last 3 years the vaccine had induced anaphylaxis.

Table 6. *Estimated incidence rates of adverse post-vaccinal reactions in different breeds of previously unvaccinated cattle*

	Percentage incidence	
Breed	Rinderpest-like reactions	Aggravations of latent disease
Ayrshire	0·15	0·18
Friesian	0	0·10
Guernsey	1·61	0·12
Hereford	0	0·31
Jersey	0·64	0·09
Red Poll	0·64	0·02

Table 7. *Batches of lapinized rinderpest vaccine which induced rinderpest-like reactions in cattle*

Batch Number	Number of cattle vaccinated	Number of rinderpest-like reactors
387/54	3,570	47
400/54	14,250	52
411/54	7,262	7
413/54	8,640	20
18/55	10,500	61
19/55	2,250	4
22/55	7,500	10
24/56	12,900	13
29/56	9,375	3

Retests of vaccine batches

Nine out of 109 batches of lapinized rinderpest vaccine used in Kenya in the period under review evoked rinderpest-like reactions in cattle (Table 7). Ampoules of the first four batches were retested in rabbits and cattle. The results agreed closely with those of the original batch tests and there was no evidence that the vaccine differed from normal lapinized rinderpest virus. Further retests were regarded therefore as unnecessary.

Recovery of virus from reacting cattle

Seventeen attempts were made to isolate virus from cattle with rinderpest-like reactions. All attempts from samples sent to the laboratory failed. Four of the seven attempts to isolate virus by bleeding the reacting cattle and immediately inoculating the blood into rabbits brought to the farm succeeded. One isolate was from an Ayrshire (A), one came from a Jersey (J), and two were from Guernsey cattle (G 1, G 2).

Suspensions of tissues from the infected rabbits were inoculated subcutaneously into cattle which were housed along with uninoculated susceptible cattle. Neither the 16 inoculated cattle nor the 16 uninoculated controls exhibited a clinical response and there was no evidence that the isolated viruses were virulent. The cattle were challenged 14 days later by the injection of 10,000 CID_{50} virulent rinderpest virus. The inoculated group proved to be immune whereas the control cattle were all susceptible and 12 died.

In other words, the four isolated viruses were genotypically 'normal' lapinized rinderpest viruses in that they infected and induced pathognomonic lesions in rabbits; they infected grade cattle without stimulating a clinical reaction yet induced immunity to virulent rinderpest virus; and they were non-contagious.

DISCUSSION

Adverse reactions in Kenya cattle after vaccination with lapinized rinderpest virus fell into four categories: rinderpest-like, aggravation of latent protozoal infections, transient spermatolysis and anaphylaxis. The most serious were the aggravations of latent infections because of the attendant high case mortality rate, which approached 40 %. The commonest were rinderpest-like reactions which were without serious sequelae except in pregnant animals.

The over-all incidence of adverse reactions was 9 per 10,000 cattle vaccinated, which compares favourably with the incidence of adverse reactions in domestic animals and man given other attenuated virus vaccines. However, the total number of cattle vaccinated was not the true population at risk. The first three categories occurred only in animals which were being vaccinated for the first time and were directly attributable to the effects of virus multiplication. Accordingly the true population at risk was confined to rinderpest-susceptible cattle, which were estimated as being one-third of those presented for vaccination. Moreover, adverse reactions were not evident in *Bos indicus* cattle. The real incidence rate therefore approaches 3 per 1000 cattle at risk. This figure can be validly compared with the 95 % incidence in zebu cattle given caprinized vaccine (Daubney, 1949*b*) because expected post-caprinized reactions would be classified in this paper as adverse. In fact, adverse reactions associated with caprinized vaccinations are measured by the case mortality rate, which is 2 % in zebu cattle and up to 7 % in European breeds. The case mortality rate in cattle with adverse reactions after vaccination with lapinized rinderpest virus was nil in zebu cattle and 7·2 % in European breeds. The similarity in the figures is misleading because the caprinized vaccine case mortality rate is virtually synonymous with the over-all mortality rate. The lapinized vaccine case mortality rate differed dramatically from the overall mortality rate of 0·006 % of cattle vaccinated or 0·05 % of cattle at risk. Lapinized rinderpest vaccine was therefore safer than caprinized vaccine.

The only serious sequel to rinderpest-like reactions was abortion. Unfortunately the significance of the pregnant animal was realized too late and the over-all abortion rate in pregnant animals could not be determined. Nevertheless, it would appear to be advisable to ensure that primary vaccination is carried out when animals are immature. Susceptible pregnant animals should not be vaccinated.

The sequel to a simple interaction between a virus and a susceptible host is largely governed by two factors, the virulence of the virus and the innate resistance of the host. The virulence of a virus for a particular host is probably a genetic characteristic (Burnet, 1955) and serial passage of a virus in a foreign host selects spontaneously occurring mutant genotypes which are avirulent for the natural host. The selection is fortuitous. For example, Koch (1897) passaged rinderpest virus simultaneously in goats and sheep. In goats, a strain slightly avirulent for cattle developed, but in sheep the strain developed an enhanced virulence for cattle. Edwards (1928) rediscovered the phenomenon of attenuation by serial passage in goats and thus pioneered the present types of rinderpest virus vaccines. Conversely Minett (1940) was unable to select an avirulent genotype despite more than 175 serial passages in goats. The attenuated rinderpest viruses used today as vaccines are considered 'fixed' and virulence for cattle is not regained despite serial passages in cattle (Nakamura, Fukusho & Kuroda, 1943; Waddington, 1945). Nevertheless, Ramon (1956) cited the Kenya incident reported by Brown *et al.* (1955) to support his argument that living virus vaccines should not be used. He postulated that such vaccines created carriers, and reactors to the virus caused new foci of infection and thus propagated the disease instead of assuring its prophylaxis. In other words, the stability of the virulence of the virus was variable. Our findings refute Ramon's conjecture, because the viruses which we recovered from reacting cattle were all genotypically lapinized rinderpest viruses.

The evidence strongly suggests that the true variable was the innate resistance of the cattle. Early workers recognized differences in innate resistance to rinderpest between local races or breeds of cattle (Seifman, 1866; Varnell & Pritchard, 1866) and since then the phenomenon has been well documented from all parts of the world. The differences were not correlated with the species. As a generalization we accept the current hypothesis regarding variations in innate resistance of cattle to rinderpest first mooted by Mornet (1948), and which was expressed by Henning (1949) as an evolution by a process of natural selection from ancestors which had survived previous visitations of the disease; a hypothesis which fulfils Theobald Smith's concept (1934) of the host-parasite relationship's equilibrating to the mutual advantage of both the parasite and the host. East African short horned zebus possess a marked innate resistance to rinderpest, and cattle of European origin have a low innate resistance (Cornell & Evans, 1937). This difference was clearly revealed in the survey but in addition shades of innate resistance were found within the non-resistant group. The important factor governing the degree of resistance appeared to be familial, because rinderpest-like reactions tended to occur in related cattle. Neither the sex nor the age of the cattle influenced the incidence of reactions.

When the virus–host interaction was complicated by the presence of a latent protozoal infection the sequel was serious. Aggravation of a protozoal infection occurred only in rinderpest-susceptible stock and therefore would appear to be a direct result of virus multiplication. The phenomenon is familiar to older veterinarians who used the serum-virus simultaneous method for protecting cattle against rinderpest and Mornet, Gilbert, Orue & Thiery (1955) have also observed 'flare-ups' in cattle vaccinated with lapinized rinderpest virus in French West Africa. The mechanism has never been explained.

SUMMARY

A survey embracing all cattle vaccinated in Kenya with lapinized rinderpest virus between 1 January 1954 and 30 June 1956 revealed an over-all incidence rate of adverse reactions of 0·09 %. The real incidence rate approached 3 per 1000 cattle because only susceptible cattle were at risk. Four types of reactions were recognized. The most serious, because of the attendant high case mortality rate, was aggravation of latent protozoal infections. The commonest reactions were rinderpest-like without serious sequelae except in pregnant cows, many of which aborted. Transient spermatolysis was observed in six vaccinated bulls and anaphylaxis was recorded rarely.

The incidence of rinderpest-like reactions was primarily influenced by the innate resistance of the cattle. The viral strains recovered from reacting cattle were genotypically unchanged.

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