THE CIRCULATION OF RIFT VALLEY FEVER VIRUS IN SENTINEL ANIMALS IN SAUDI ARABIA: A RETEROSPECTIVE COHRT STUDY

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ABSTRACT

Rift Valley fever (RVF) is a serious life-threatening disease associated with severe clinical signs and health consequences for humans and a wide range of domestic animals. In September 2000, a RVF outbreak was reported in Jazan region south-west Saudi Arabia with 886 human cases including 124 deaths. Since then a control program has been in place which mainly involved, vector control, sustaining vaccination campaigns and sentinel surveillance system. In this research, we conducted a retrospective cohort study of 11 sentinel herds, to investigate the circulation of RVFV in high-risk area from 2004 to 2018. Additionally, we examined the association between vaccination against RVF and the risk of disease infection by conducting a pooled analysis of 18287 cases from cross-sectional surveys. The results indicated that, thirty-six (0.1%) out of 330 sentinel animals, were laboratory diagnosed as having RVF infection. 16 (44.4%) were goats and 20 (55.6%) were sheep. The highest prevalence of RVFV antibody was found in Alardah's herd 13(36.1%), followed by Abuareesh, and Alqunfidah 6(16.7%) and 5(14.0%) respectively. These results, clearly provide evidence for the circulation of RVFV in the region during interepidemic period. Interestingly, in local herds- that were previously vaccinated against RVFV and exposed to the same level of hazard as sentinel- the risk of RVF exposure was much lower (0.29 cases per 100 animals) as compared to the risk in sentinel animals (13.45 cases per 100 animals). risk ratio is (0.02) P-values <0.05, 95% confidence interval (cl).

This article concludes that, despite the insufficient vaccination coverage that occurred due to some restrictions associated with the use of live attenuated RVF vaccine, the vaccination program appeared as highly effective in preventing future outbreaks.

INTRODUCTION

RVF is a serious infectious disease in humans and a wide range of domestic ruminants, caused by mosquito-borne virus that belongs to the family *Bunyavirridae*, genus *phlebovirus* [1]. It was first reported among livestock in Kenya in 1931, since then it has been reported in the Arabian Peninsula, particularly in Saudi Arabia and Yemen in the year 2000 [2,3]. This outbreak was the first appearance of the RVFV outside Africa and raised concerns about the potential incidence and the establishment of the disease in new environmental conditions that have not ever experienced the disease before [4]. The virus apparently introduced to Saudi Arabia during the religious festivals (Eid Aladha) through importation of live animals from African Horn countries, because, the virus isolated during the 2000 outbreak had an RNA sequence similar to the virus that was isolated in 1997-1998 East African outbreaks **[5], [6].** By the year 2000, Jazan region-South west Saudi Arabia- has had the hardest hit by the disease. Out of the total of animal cases (65.6%) occurred in Jazan, (26.9%) in Asir and (7.5%) in Alquenfeda, the infection rate was (23%, 8.7% and 2%) in Jazan, Asir and Alquenfeda, respectively **[7].** The adverse effects of the disease and the serious socio-economic impacts obliged the relevant veterinary authorities in Saudi Arabia to devote an effective control program, including but not limited to : 1) vector control 2) vaccination of nonpregnant animals above six months with live attenuated RVF vaccine 3) surveillance systems based on sentinel herds.

Globally, sentinel surveillance systems have been successful in early detection of virus circulation in high risk areas due to its ability to focus on a specific disease [**8**]. Likewise, in Saudi Arabia, since 2004, ruminants such as goats and sheep have been used as sentinels for monitoring RVFV activity in high risk zones where occurrence is most probably as the result of vector presence. However, the key objectives of the current study had two parts: 1) to investigate the circulation of

RVFV in high risk areas. 2) To estimate the effectiveness of the current vaccination strategy that based on routine vaccination with live attenuated RVF vaccines for nonpregnant ewes, by studying the relationship between vaccination and the risk of RVF infection in both of sentinel herds as non-vaccinated group and local herds that exist in the same area as vaccinated animals.

MATERIALS AND METHODS

A- METHODS OF DATA COLLECTION

Jazan region is located on the farthest south-west Saudi Arabia between longitudes 41.0213ºE and 43.3377º E and latitudes 16.0943ºN and 18.3281ºN, near the Yemeni borders which represent the southern and eastern borders. The Red Sea borders the region from the west for a distance of (330) Km2 along the sea coast, while Asir region from the north. The region covers an area of 40.457 KM2 and it is divided into 13 governorates and 31 districts. The terrain of the region varies and consists of mountains, coastal and fertile plains [**9**]. The existence of ecological diversity pattern and different types of vegetation, listed the region among the richest areas in Saudi Arabia with animal biodiversity[**10**]. Moreover, the considerable amounts of rainfall, besides the hot humid climate conditions and fields that are irrigated from Wadies, provide an ideal habitat for RVF vectors [**11**].

2.1 study design and data collection

This study had two components: the first was a retrospective cohort study carried out on sentinel animals to investigate the circulation of RVFV in high risk zones. The second was a pooled analysis of cross-sectional surveys that targeted local herds at risk of the disease to estimate the risk of RVF in vaccinated animals.

2.2 Sentinel herds

Sentinel animals are unvaccinated animals, related to the local breeds and imported from regions free from RFV infection in 2004 to investigate the potential circulation of RVFV during inter-epizootic period. These animals were ear tagged with plastic numbers and regularly subjected to IgM and IgG antibodies tests against RVF before they were placed in ideal habitats where virus activity might have been

expected [**12**]. These herds were established in eleven districts include: Alarda- Alhurath–Abuareesh- sabia- Almasarha- Bulgazi –Baish- Mahaeel- Mejardah- Mekhwa- quenfeda. (**table 1**).

Table 1: Sentinel Herds investigations

Number of Herds	Number of animals in each Herd	Total number of animals	Sampling program
11 herds	30 animals	330	Monthly during rainy season

2.3 Samples Collection:

Sera from sentinel herds were collected on a monthly basis during the study period. Whole blood samples (8.0 mL) collected into Serum-separating tubes (SST), from sheep and goats. The blood for serum was taken to the refrigerator and placed vertically until the following day. The tubes were centrifuged at 3000g for 15 minutes and clear serum was pipetted off into sterile barcoded cryovials.

2.4 Laboratory Examinations:

Serological Tests:

The serum samples were analyzed using the (ID Screen® Rift Valley Fever Competition Multi-Species Capture) for the detection of both IgG and IgM to Rift Valley fever virus. The positive serum samples for RVFV virus-specific antibodies were then tested for IgM antibodies using the ID Screen® Rift Valley Fever IgM [**13**]. The commercial ELISA kits were performed according to the producer's description.

2.5 Data Analysis:

The data were analyzed with iNZight software version number 3.3.6 ,2019. The following variables for each sample were recorded: species, sex, site, district, clinical signs, IgM and IgG. The X chi square test is used to examine the relationships among variables.

RESULTS

From 2004 to 2018, our sentinel surveillance system identified nine herds as seropositive for RVF infection out of eleven herds. Out of 330 sentinel animals included in the study, 36 (10.9%) were found sero-converted to RVF. Most cases of RVF were reported in Alardah, Abuareesh, and Alqunfidah, (36.1%), (16.7%) and (13.9%) respectively table (2). Fig 1.

As illustrated in Fig (2) a very low virus activity was reported between 2014-2016. Furthermore, with the exception of Abuareesh's sentinel herd no one else has affected in the same period. In contrast, the critical periods of virus circulation were observed from 2012-2014 and 2016-2018.

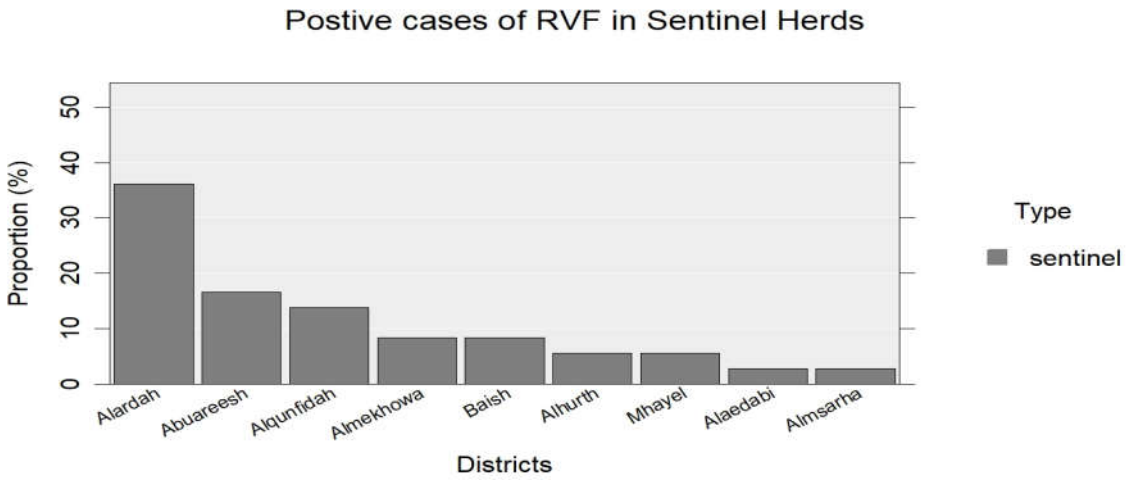

Fig 1: Distribution of RVF positive cases in sentinel animals

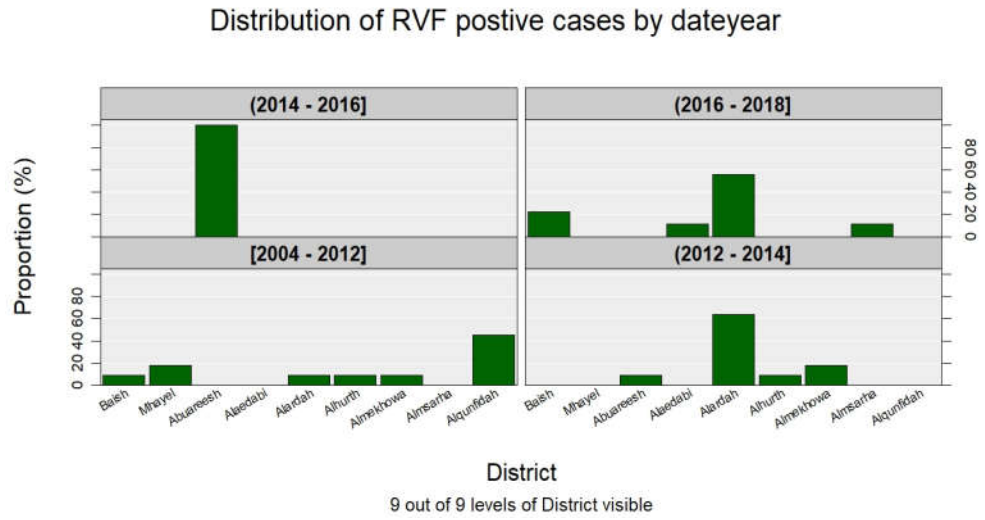

Fig 2: Distribution of RVF positive cases by year decade

Table 2: Distribution of RVF positive cases in sentinel herds

	Alardah	Abuareesh	Alqunfidah	Almekhowa	Baish	Alhurth	Mhayel	Alaedabi	Almsarha	Total
Count	13	6	5	3	3	2	2	1	1	36
Percent %	36.111	16.667	13.889	8.333	8.333	5.556	5.556	2.778	2.778	100

As shown in Fig (3) the distribution of RVF does not depend on animal species**.** no significant difference was observed in the rate of infection between species. Out of 36 positive cases 16 (44.4%) were goats and 20 (55.6%) were sheep.(p-value = 0.11628)

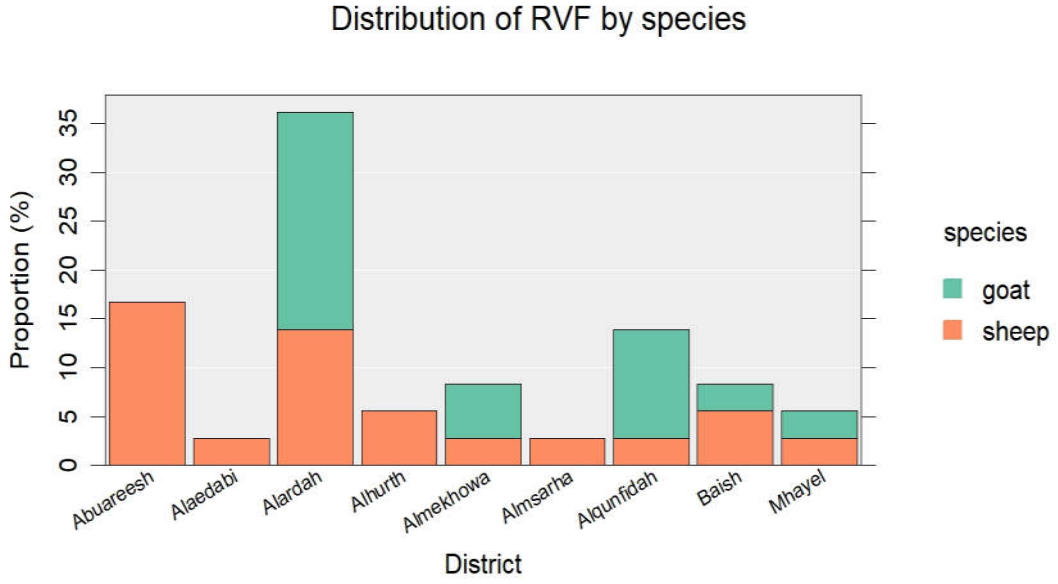

Fig 3: Distribution of RVF positive cases by species

Interestingly, the assessment of clinical signs in sentinel animals revealed that most positive cases of RVF were diagnosed without clinical signs. Thirty-two (88.9%) out

of thirty-six animals were diagnosed as positive as clinically healthy. While, only two cases out of the total (5.6%) were aborted and seroconverted due to RVF in Alardah and Mhael FIG (4).

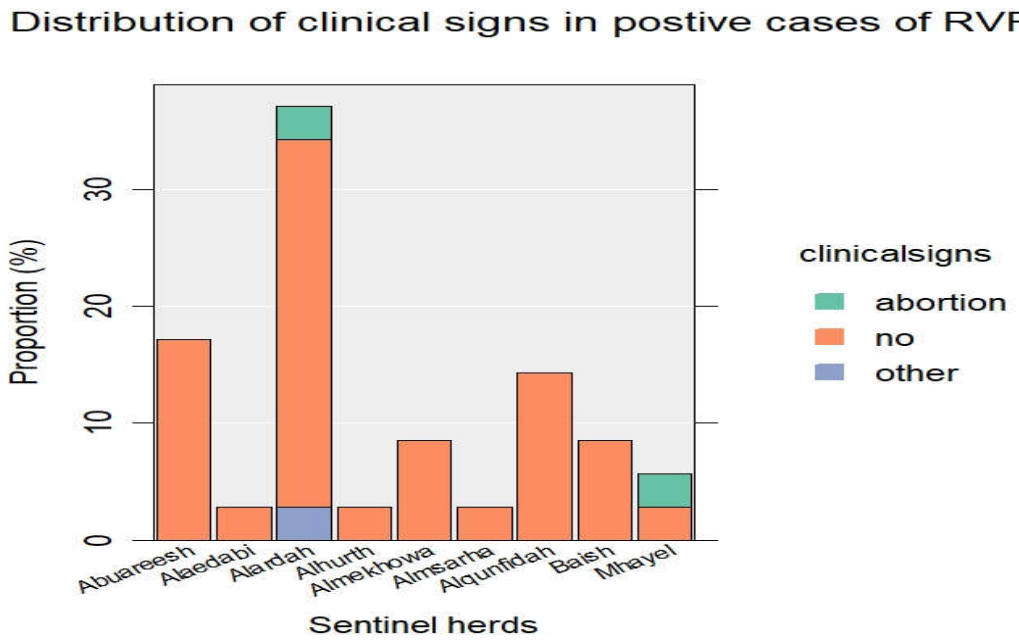

FIG 4: clinical signs

Analysis of the cross-sectional data suggests that the risk in vaccinated animals is 53/18287 =0.29 cases per 100 animals. In contrast, the risk of RVF infection in sentinel herds is 36/330=10.9 cases per 100 animals. The risk ratio is estimated to (0.03), P values <0.05, which tells us that vaccination against RVF seems to be protective. (**Table 3**)

Table 3:

	Positive cases of RVF	Negative cases of RVF	Total
Local herds (vaccinated animals)	53	18234	18287
Sentinel herds (unvaccinated animals)	36	294	330
Total	89	18528	18617

DISCUTION

It is apparent that the ecological patterns and climate conditions in Jazan region were favorable to the persistence and endemicity of RVFV as long as the virus remains in mosquito breeding sites for a long time once introduced [**14**]. As the result, our sentinel surveillance system that involved both of sheep and goats has identified the existence of recent RVFV circulation in Jazan, Aseer and Alquenfidah. Furthermore, this study confirmed that, out of 375 animals studied, 36 were identified as positive for RVF. The estimated risk of infection was (0.13%). These findings are inconsistent with the study performed in Zambia by [**15**] who reported a very low rate ranging from (0.03-.08%).

Through this study, it had been shown that, both sheep and goats were involved in RVF infection, despite, no significant difference in exposure was found between sheep and goats,16 (44.4%) and 20 (55.6%) respectively. These results are in line with previous research findings performed in Ijara and Marigat district, Kenya between 2009-2012, where a similar result were described [**16**].

Although, it has been observed that, most positive cases were reported in Alardah, Abuareesh, and Alqunfidah, none of the sentinel animals in Almjardah and Sabya showed any seroconversion to RVF over the study period**.** These herds should be relocated as the result of no virus circulation ever been detected.

Currently, the live attenuated vaccine (Smithburn strain) has been used as the gold standard vaccine in Jazan region since the outbreak of 2000. According to manufacturer's instructions, the vaccine can cause abortion or fetal malformation in a

small percentage of animals, particularly sheep, as well as a slight febrile reaction that may occur on the second to fourth day following inoculation. Therefore, the use should be restricted to nonpregnant animals above six months of age [**17**]. This situation has negatively affected vaccination coverage and herd immunity. consequently, controversy about the effectiveness of the vaccination program persists. However, in this study we filled the aforementioned knowledge gap by examining the association between vaccination and the risk of RVF exposure in both of sentinel herds as non-vaccinated group and local herds as vaccination group. Over the entire study period, it has been found that the risk of RVF infection in zones where vaccination has been practiced is significantly lower than the risk in sentinel animals OR= (0.03). These results confirmed the effectiveness of vaccination and supporting the recommendations for continuing the immunization with a RVF live attenuated vaccine to prevent high risk populations despite its drawbacks. These adverse effects, stressed the need for producing new vaccines with an excellent safety profile to bridge the gap in safety and immunity **[18]**

CONCLUSION

To sum up, we conclude that RVFV is continuously circulating in the region during interepidemic period, even in the absence of clinical cases. Additionally, the study findings strongly filled the knowledge gap in the feasibility of vaccination program and provides new insight into a compelling rationale to increase compliance with recommendations for routine use of RVF vaccine to prevent major outbreaks.

Competing Interests

The author declares that there is no conflict of interest regarding the publication of this paper.

دراسة استرجاعية في القطعان الكاشفة لرصد نشاط فيروس حمى الوادي المتصدع في المملكة العربية السعودية

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الخلاصة

مرض حمى الوادي المتصدع مرض خطير من الامراض المهددة لحياة الانسان ويتسبب في حدوث كثير من الأعراض والمضاعفات الوخيمة للانسان والحيوان. في عام 2000 تعرضت منطقة جازان والتي تقع في الجزء الجنوبي الغربي من المملكة العربية لوباء مرض حمى الوادي المتصدع، حيث بلغ عدد المصابين من البشر آنذاك 886 شخص توفي من بينهم 124 شخص. منذ ظهورالمرض في المملكة تم إنشاء برنامج متكامل للسيطرة على المرض يعتمد بصورة أساسية على مكافحة نواقل الأمراض وحملات التحصين المنتظمة إضافة الى نظام التقصي الوبائي للحيوانات الكاشفة. من خلال هذا البحث تم عمل دراسة في القطعان الكاشفة والتي تضمنت 11 قطيع كاشف بهدف دراسة النشاط الفيروسي لمرض حمى الوادي المتصدع في المناطق عالية الخطورة والمعرضة للاصابة بالمرض وذلك خلال الفترة من 2004-2018. أيضاً تم دراسة العلاقة بين التحصين ضد مرض حمى الوادي المتصدع وخطر الإصابة بالمرض وذلك عن طريق تحليل بيانات عدد (١٨٢٨٧) حالة تم جمعها من خلال برامج المسح الوبائي المستعرض. أشارت نتائج هذه الدراسة الى ان ٣٦ راس (٠.١%) من أجمالي ٣٣٠ راس من القطعان الكاشفة تم تشخيصها في المختبر كحالات إيجابية لمرض حمى الوادي المتصدع. من بين هذه الحالات ١٦ حالة من الماعز (٤٤.٤%). بينما بلغ عدد الحالات في الضأن ٢٠ حالة (٥٥.٦%). أعلى نسبة انتشار للأجسام المناعية لفيروس حمى الوادي المتصدع كانت في القطيع الكاشف بمحافظة العارضة ١٣ (٣٦.١%)، يتبعها القطعان الكاشفة في محافظات ابوعريش ٦ (١٦.٧%) والقنفذة ٥(١٤%). هذه النتائج تؤكد بصورة واضحة على وجود نشاط فيروسي لمرض حمى الوادي المتصدع في المنطقة خلال الفترة ما بين الوبائيات. أيضاً أثبتت الدراسة أن قطعان المربيين في المناطق العالية الخطورة والتي تم تحصينها مسبقاً بلقاح حمى الوادي المتصدع، خطر تعرضها للإصابة بالمرض اقل بكثير (٠.٢٩ حالة في كل ١٠٠ حيوان) مقارنة بخطر الإصابة في الحيوانات الكاشفة والتي تقدر نسبة خطر الإصابة بها (١٣.٤٥ حالة لكل ١٠٠ حيوان)، نسبة الخطر (٠.٠٢). مع وجود فرق معنوي عند مستوى احتمال اقل من (0.05%) واختبار ثقة 95%. ختاماً خلصت هذه الدراسة الى أنه بالرغم من وجود قصور في تحصين كافة افراد القطيع عالية في حماية القطعان بسبب بعض العيوب في اللقاح الحي المضعف، الا أن برنامج التحصين يظهر كفاءة من الاندلاعات الوبائية في المستقبل.

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