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Caprine Respiratory Mycoplasmosis (*Contagious Caprine Pleuropneumonia CCPP*)- A Global Perspective of the Disease, Epidemiology, Diagnosis, Chemotherapy and Immunization: A Review

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ABSTRACT

Mycoplasma infection of the respiratory tract of goats is prevalent worldwide including the South Asian sub-continent. Owing to intensive and large scale goat farming, the incidence of the disease is on an increase. Among various species of mycoplasma, *Mycoplasma capricolum* subspecies *Capri pneumoniae* is increasingly incriminated in *Contagious Caprine Pleurapneumonia* (*CCPP*) in goat populations with considerable economic fallout in the form of high morbidity and mortality. The disease manifestations in caprines are recorded as anorexia, high febrile reaction and respiratory embarrassment in the shape of clinical dyspnoea, polypnea, paroxysmal cough and sero-purulent nasal discharges. The disease is thus contracted by the healthy animals through aerosol, contaminated feed and water sources in the herd premises, without a protective immunity and that the conferred immunity in recovered cases being short-lived. The true lesions of *CCPP* are confined to the lung alveolar tissues of infected goats, which distinguish it from other respiratory diseases of small ruminants caused by the members of the *Mycoplasma mycoides* cluster. Atypical pneumonia caused by the mycoplasma infection of goats, also known as *Contagious Caprine Pleuropneumonia* (*CCPP*) has been more often reported from Africa and Asia than Europe. Classical, acute *CCPP* attributed to *Mycoplasma capricolum* subsp. *Capri pneumoniae*, originally known asthe F38 biotype (World Organisation for Animal Health, 2008) causes heavy kid mortality. Two other organisms in this group, *M. mycoides* subsp. *capri* and *M. mycoides* subsp. *mycoides* large-colony type, can cause disease in small ruminants that clinico-pathologically mimics *CCPP* but may have extra pulmonary signs and lesions, sometimes. *Mycoplasma Capri pneumoniae* and other members of the *M. mycoides* cluster cross-react in serological tests and share biochemical and genetic similarities. The most favourable epidemiological scenario in the Sub-continent is the hot humid climate during monsoons. The diversity and multi-etiological subspecies involved in the disease is detrimental in the development of an effective vaccine even though in some places a liquid vaccine is presently in use. At other places, anti-mycoplasmal antibiotics of aminoglycoside and fluoroquinolone and perhaps the macrolide groups remain to be the main option in preventing flock mortalities.

Key words: *CCPP*, Mccp, Mycoplasmostatic antibiotics, *Mycoplasma* spp, Vaccine.

Microbiologically the mycoplasmae are gram-negative mollicutes, classified between bacteria and viruses, consisting of cells bound by a plasma membrane and an indiscrete cell wall. These are extracellular pathogens with an affinity for mucous membranes, where they exist as commensals or pathogens. Pathogenic mycoplasmae have a predilection for the respiratory system, urogenital tract, mammary gland and serous membranes. Most of the members of the *C. mycoplasma mycoides* cluster group are the importantpathogens for small ruminants. This group comprises six species and subspecies. In small ruminants, they are known for respiratory disease, kerato-conjunctivitis (Shaheen, *et al*., 1997; Shaheen *et al*., 2000), arthritis, genital disease and mastitis (Nicholas, 2002). Some of these Mycoplasma species can cause severe and contagious diseases in Goats with significant economic impact (Cottew *et al*., 1987). Of the many Mycoplasma diseases, *Contagious Caprine Pleuropneumonia* (*CCPP*) is a highly fatal disease that occurs in Eastern Europe, the Middle East, Africa and Asia (Table 1) (Kopcha, 2005). *Contagious Caprine Pleuropneumonia* (*CCPP*), an OIE List B disease is associated with *Mycoplasma capricolum* subspecies *Capri pneumoniae* (Radositits *et al*., 2007). *Contagious Caprine Pleuropneumonia*

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(*CCPP*) is a disease affecting Goats and some wild ruminant species. The acute and sub-acute disease is characterised by unilateral sero-fibrinous pleuro pneumonia with severe pleural effusion (OIE, 2014). A variety of mycoplasmae, including *M. agalactiae*, *M. mycoides, M. ovipneumoniae* and *M. Mycoides* var. *capri* have also been isolated from affected goats culminating into a spectrum of syndromes including fibrinous peritonitis, pneumonia, arthritis, mastitis and abortions (Radositits *et al*., 2007). The seroprevalence of the disease in India is recorded to be 33.67 percent (Ingle *et al*., 2008). In India, the antibodies against the *Mycoplasma capricolum* subspecies *capri pneumoniae* have been isolated from Gujarat, Himachal Pradesh, Uttar Pradesh, Maharashtra, Jharkhand and Tripura. Prevalence studies across the enzootic area in Africa and Asia revealed seroprevalence of 14.6% in Ethiopia, whereas in Kenya individual seroprevalence varied from 6 to 90 %. In Mauritius, where *CCPP* emerged in 2009, nine of 62 herds tested positive, whereas seroprevalence varied between 2.7% and 44.2% in the other districts investigated in northern Pakistan (Peyraud *et al*., 2014). The most favourable epidemiological scenario is the hot humid climate during monsoons in South Asia. Africa and the Middle East have supposed to pose a significant threat to many disease-free areas including Europe. Furthermore, the molecular epidemiology of *CCPP* (MLSA) has revealed its identification in Tajikistan and China (Manso-Silvan *et al*., 2011). It was more likely that the disease might have been endemic to these countries for a long time, as supported by historical clinical descriptions (Fig 1; Table 1).

The molecular epidemiology, cultural characteristics and transmission

CCPP is caused by *Mycoplasma capricolum* subsp. *Capri pneumoniae* (Mccp). Taxonomically Mccp belongs to the so-called mycoides cluster (Manso-Silvan *et al*., 2007) and it received its name only recently (Leach *et al*., 1993). Its closest relatives are *Mycoplasma capricolum* subsp. *capricolum* and *Mycoplasma leachii,* which may cross-react with Mccp, but the other members of the mycoides cluster, such as *Mycoplasma mycoides* subsp. *capri* or *Mycoplasma mycoides* subsp. *Mycoides* and even *M. ovipneumoniae* may also share similarities. *M. ovipneumoniae* is primarily responsible for atypical pneumonia in goats and predispose the animals to other pneumonia-causing bacteria and viruses (Evermann, 2017). Mccp is highly fastidious and faint turbidity in PPLO liquid medium or colonies on solid PPLO

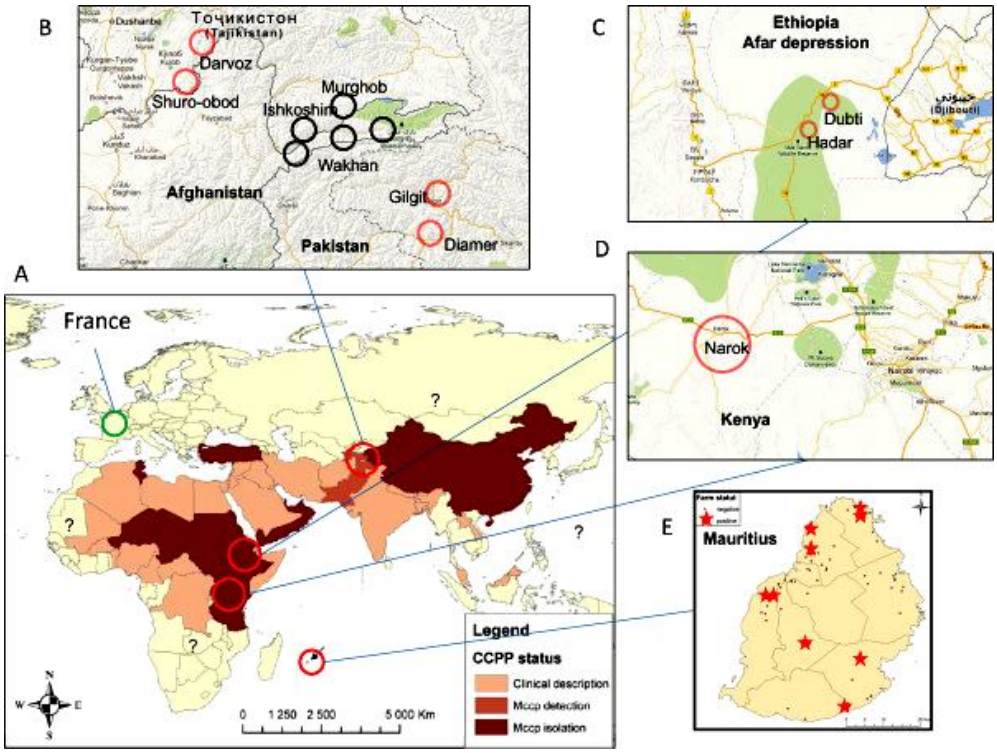

Fig 1: Map showing the countries and regions studied in the *CCPP-cELISA* serological survey (Peyraud *et al*.2014).
A: World map showing the various locations. The green circle represents France, where the specificity of the test was validated.
B: Central-Asian location around the Wakhan district in Afghanistan. C: Afar depression in Ethiopia. D: Narok district in Kenya.
E: Reunion Island. The dots indicate the locations of the sampled herds that tested negative by CCPP cELISA.

agar medium enriched with horse serum may appear only after 3-15 days (Shaheen *et al*., 2001). *M. Mycoides*-var-*capri* is more often associated with *CCPP* in India. Isolation is often unsuccessful and detection may be easier with specific molecular methods such as the PCR (Woubit *et al*., 2004; Samiullah, 2013). Mycoplasmas are the smallest free-living fastidious bacteria intermediate. They are about 300 nm in diameter, bound by a triple-layered membrane and unlike conventional bacteria, they don't have a rigid cell wall of murin (Robinson, 1997). Their genome size is only one-sixth to one-third of that of *Escherichia coli* (Bascunana, *et al*., 1994). Mycoplasmas are phylogenetically related to gram-positive bacteria with low G + C content (Razin, *et al*., 1983). The Mycoplasma mycoides cluster has two rRNA operons in which intraspecific variations have been demonstrated (Heldtander *et al*., 2001). *Mccp* was once thought to be a homogenous taxon (Heldtander *et al*., 2001; Abu-Groun *et al.,* 1994) but the discovery of two molecular markers showed some degree of heterogeneity among strains that opened a further channel for studies on the molecular epidemiology of *CCPP*. A typing method with an improved resolution based on Multi-Locus Sequence Analysis (MLSA) developed to trace new epidemics and to elucidate whether the recently identified cases in continental Asia were due to the recent importation of Mccp, proved to be sensitive. The H2 locus, a polymorphic region already in use as a molecular marker for *Mccp* evolution, was complemented with seven new loci selected according to the analysis of polymorphisms observed among the genome sequences of three Mccp strains. Asian distinct strains were including the two new strains, were analysed by MLSA resulting in the discrimination of 15 sequence types based on 53 polymorphic positions. Polymorphisms in Mccp strains can be used as epidemiological markers for *CCPP* in smaller geographical areas and to study the molecular evolution of this species (Nicholas, 2002). Eleven polymorphic positions were observed in the sequence of 2400 bp long fragments, obtained from 19 Mccp strains from various geographical locations (Lorenzon *et al*., 2002). Similarly, in molecular typing, a good correlation between MLSA (multi locus sequence analysis) groups and the geographic origins of the Mccp strains was observed (Samiullah, 2013).

Table 1: Geographical distribution of *Caprine Contagious Pleuropneumonia* worldwide.

Country	Incidence	Country	Incidence
Africa		Middle East and	
Angola	+	Arabian Peninsula	
Benin	+		
Cameroon	+++	Bahrain	++
Chad	++	Iran	++
Djibouti	?	Iraq	?
Ethiopia	++	Jordan	+
Guinea Bissau	+	Kuwait	++
Kenya	+	Lebanon	+
Libya	+	Oman	+++
Mali	?	Qatar	+
Mauritania	+	Saudi Arabia	+
Niger	?	United Arab	+
Nigeria	?	Emirates	++
Senegal	+	Yemen(Arab	++
Somalia	++( )	Republic)	+++( )
Sudan	+++	Yemen(P.D.R	)(
Tunisia	+	South Asian	+
Uganda	?	subcontinent	+
Zaire	?	Bangladesh	?
Americas		India	(?)
Brazil	+?( )	Nepal	+
Dominica	+	Pakistan	+
		Europe	+
		Greece	+
		Malta	
		Turkey	

Source: FAO/WHO/OIE Animal Health Yearbook, 1986.

(+): Exceptional occurrence; + ?: Serological evidence only, no clinical disease; +: Low sporadic occurrence; ?: Suspected but not confirmed; ++: Enzootic; ( ): Confined to certain regions; + + +: High occurrence;) (: Ubiquitous.

CCPP is transmitted directly by an aerogenic route through contaminated droplets of cough and nasal secretions (Thiaucourt *et al*., 1996). The outbreak of the disease follows the introduction of an infected animal into a group of susceptible goats (OIE, 2008). The disease is readily contagious and a short period of contact is enough for successful transmission through coughing (Thiaucourt and Bolske, 1996; OIE, 2008). No evidence of indirect contact has been shown as the organism is highly fragile in the environment (Manso-Silvan *et al*., 2007). It is quickly inactivated within 2 min at 60°C but can survive for more than 10 years in frozen infected pleural fluid (OIE, 2008). Disease outbreak may occur after heavy rain, animal transportation over a long distance (OIE, 2008), poor climatic conditions and primary infections (Thiaucourt and Bolske, 1996). In most places in the South Asian sub-continent, the disease is usually prevalent during the monsoon season and disappears during the dry hot summer season (Giadinis *et al*., 2008). Formaldehyde can inactivate Mccp in 30 sec. at a concentration of 0.05%. A solution of 1.0% phenol can inactivate the organism within 3 min (OIE, 2008). In primary infected Goats, *CCPP* lasts for about two days with high mortality (Mc Martin, *et al*., 1980) while in other cases it may last for several days (OIE, 2008). However, in an experimental infection model, Mccp was not isolated from the infected lungs of goats eight-week post-infection due to the development of humoral immunity (March, 2002).

Clinical manifestations, lesions and diagnosis

The typical clinical signs attributed to *CCPP* are hyperpyrexia (41-43°C), high morbidity and mortality rates in susceptible herds irrespective of age and sex. The development of dyspnoea sometimes with grunting and moist rales, continuous nasal discharge that gradually turns seropurulent is specific to this disease besides anorexia and abortion (Nicholas, 2002; OIE, 2008). In peracute cases, goats may die within one to three days with minimal clinical signs (Nicholas, 2002). Typical *CCPP* lesions occur in the thoracic cavity only (Mondal *et al.,* 2004) and sometimes affected lungs have abundant pleural exudate and conspicuous pleuritis (Thiaucourt and Bolske, 1996). The lungs show a peculiar marble shape when examined grossly. Coughing is irregular and nasal discharge is often absent initially (OIE, 2008). Affected lungs degenerate into a voluminous abscess as a consequence of secondary bacterial infection (Thiaucourt and Bolske, 1996). Affected lungs become hepatised and take on a port wine colour (Thiaucourt and Bolske, 1996), with pea-sized yellow nodules surrounded by congestion (OIE, 2008). The pleural cavity contains an excess of straw-coloured fluid with fibrin flocculations (Kaliner and MacOwan, 1976; Wesonga, 1993; OIE, 2008; Rurangirwa and McGuire, 2012). Adhesions between the lung and the pleura are very common and often very thick (MacOwan and Minette, 1977). In sub-acute or chronic cases, the symptoms are very similar to acute cases, but weak (Thiaucourt and Bolske, 1996).

Confirmatory diagnosis is based on the isolation of Mccp from clinical samples of the lung (Nicholas and Churchward, 2012). The ideal sample for Mccp isolation is a pleural fluid obtained from a recently slaughtered or live infected goat (Thiaucourt and Bolske, 1996). Unlike the true *CCPP* caused by Mccp, other Mycoplasma infections can spread beyond the thoracic cavity (OIE, 2008). In the laboratory, the major problem in Mccp isolation is its slow growth and frequent contamination of the culture by other Mycoplasmas (Thiaucourt and Bolske, 1996; Nicholas and Churchward, 2012). Under an ordinary microscope, the organism has a branching, filamentous morphology in exudates, impression smears or tissue sections, while other Caprine Mycoplasmas usually appear as short filamentous organisms (OIE, 2008). Mccp and other members of the *Mycoplasma mycoides* cluster cross-react in the serological test and share biochemical and genetic similarities, so biochemical and growth inhibition tests are not reliable and specific (Awan, *et al*., 2009; OIE, 2008). The best and most accurate diagnostic method is the molecular typing of *Mccp* (Woubit, *et al*., 2004).

Cultural examination

Several media have been used for the general growth and isolation of Mycoplasmas. Mycoplasma agar and broth media are used for the selective isolation of *Mycoplasma spp*. An agar non-selective media under the product code name CC1A (Mycoplasma Experience Ltd. Product), is available that allows the development of Mccp as red colonies over seven days of incubation (MEPG online). *Mccp* has been successfully grown and isolated from infected lungs through culturing on Hayflick medium broth (H25P) (Balikci, *et al*., 2008; Cetinkaya, *et al*., 2009; Noah *et al*., 2011). Similarly modified Hayflicks media have been used for the growth and isolation of Mccp organisms (Manso-Silvan *et al*., 2011). Other than Mccp (five to seven days *in-vitro* growth), all *Mycoplasma mycoides* cluster members grow within 24-48 h *in vitro*, producing colonies 1-3 mm in diameter (Thiaucourt and Bolske, 1996). The *Mycoplasma mycoides* var *mycoides* (LC) appears as a fried egg or male nipple shaped colonies on Mycoplasma enriched (PPLO agar, marketed by Hi-media) when subsequently stained with Diene's stain.

Biochemical tests

For preliminary screening, a limited number of biochemical tests are available based on the nutritional capabilities of Mccp or specific enzyme activities (Noah *et al*., 2011). Digitonin sensitivity distinguishes Mycoplasmas from acholeplasmas, and serum digestion distinguishes members of the *Mycoplasma mycoides* cluster from all other small ruminant Mycoplasmas (FAO 2012). Phosphatase production separates Mcc from other members of the Mycoides cluster, while metabolic differences (such as maltose positive reaction for Mccp) allow differentiation between Mcc and Mccp (Barbuddh *et al*., 2005). The interspeciess variation in some biochemical reactions is often remarkable, rendering their application valueless (Jones and Wood, 1988). The lack of arginine catabolism in Mccp may help to differentiate it from

Mcc (Noah *et al*., 2011), but in some strains of Mcc arginine catabolism is reported to be lacking or very difficult to detect (Jones and Wood, 1988; Rurangirwa and McGuire, 2012a).

Serological tests

Field/farm screening for antibodies to Mccp using a latex agglutination test has been reported (Rurangirwa, *et al*., 1987) (Quite a few serological tests are available that are used in the field for the confirmatory diagnosis of *CCPP*). Indirect haemagglutination (IHA) and complement fixation tests (CFT) are used to assay the antibody response of goat to Mccp (DaMassa, *et al*., 1992). The CFT used for the detection of *CCPP* is more specific, though less sensitive than the IHA (Macowan and Minette, 1976; DaMassa, *et al*., 1992). The IHA specificity for the *Mycoplasma mycoides* cluster has been evaluated and the results were found to show cross-reactivity between these organisms (Litamoi *et al*., 1989; Cho *et al*., 1976). The latex agglutination test which detects serum antibodies in *CCPP*-infected goats is more sensitive than CFT and can be performed under field conditions using whole blood or undiluted serum with a prompt result (Wamwayi *et al*., 1989). An indirect enzyme-linked immunosorbent assay (ELISA) has been developed to screen goat serum at a single dilution of antibody to Mccp (Dighero *et al*., 1970). The specificity and suitability of ELISA for large scale testing make it an appropriate tool for the epidemiological investigation of *CCPP*. Direct antigen detection and blocking ELISA detects antibodies in the serum of naturally or artificially *CCPP*-infected goats (Dighero *et al*., 1970). Direct and indirect fluorescent antibody tests are the simple, reliable and rapid serological methods applied to clinical samples for the identification of most Mycoplasmas (Macowan and Minette, 1977). Among many, the indirect fluorescent antibody (IFA) test is the most commonly used and is applied to unfixed Mycoplasma colonies on agar (OIE 2008). The growth inhibition test (GIT) is the least sensitive and simplest of the tests available for *CCPP* diagnosis (OIE 2008). It depends on the direct inhibition of Mycoplasma growth on solid media by specific hyperimmune serum and detects primary surface antigens (Rosendal and Black, 1972; Taylor *et al*., 1997). The GIT is particularly useful in identifying Mccp because they appear to be serologically homogeneous and antiserum to the type strain produces wide inhibition zones (OIE 2008).

Molecular diagnosis

Until recently, isolation was the only way to confirm the presence of *CCPP*. A DNA probe that differentiates Mccp from other members of the *Mycoplasma mycoides* cluster was developed (Bascunana *et al*., 1994). PCR-based diagnostic systems are used for the rapid detection, identification and differentiation of the *Mycoplasma mycoides* cluster members to the serovar and strain level (Bascunana, *et al*., 1994). Sequencing of the gene for 16S ribosomal RNA has also been used to develop a PCR-based test where the final identification of Mccp is made depending on the pattern of the products after digestion of the PCR product with the restriction enzyme Pst1 (Type II restriction endonuclease) (Bolske, *et al*., 1996; Van Belkum *et al*., 2007). Species identification based on PCR of the 16S rRNA genes and restriction at positions where unique differences occur between the two operons has been demonstrated previously for Mccp (Van Belkum *et al*., 2007). An improved resolution method, MLSA (multi-locus sequence analysis) based on the analysis of several genetic markers has also been used for the identification of Mccp (Manso-Silvan *et al*., 2007). Sequence-based genotyping methods for bacterial typing are technically simple, objective-oriented and portable moreover they allow direct amplification and sequencing of the organism from clinical material (Manso-Silvan *et al*., 2007).

Chemotherapy and Immunization

The duration of the disease varies according to the environmental circumstances (OIE, 2008), however, the infected Goat can survive for more than one month or even recover if placed in good rearing conditions coupled with proper treatment (Samiullah, 2013). A number of anti-mycoplasma antibiotics and vaccines are discussed. Earlier a combination of dihydro-streptomycin sulphate (250 mg/ml) and penicillin G procaine (200,000 IU/mL) was used to treat contagious caprinepleuropneumonia caused by F38 strain of mycoplasma. A single dose of either 20, 30, 40 or 50 mg/kg body weight of the dihydrostreptomycin sulphate led to the recovery of the treated goats. The recovered goats did not transmit *CCPP* to susceptible goats housed with them for 2 months. The goats which recovered were found to be solidly immune to an in-contact challenge in which all the control goats died of *CCPP*. The treated and recovered goats were found not to be carriers of the organism (Rurangirwa *et al.,* 1981). However owing to the rapid development of microbial resistance, nowadays it is suggested that macrolides, tetracycline and quinolones are a better choice. In one study Ciprofloxacin, Tiamulin hydrogen fumarate and Oxytetracycline were ascertained to be therapeutically effective in the clinical and bacteriological recovery of *CCPP* affected kids in the order of sequence whereas Lincomycin was found to be least effective (Balikci *et al.,* 2008). However, the use of Tiamulin is restricted as it needs a long withdrawal period in food animals. In another trial study Marbofloxacin at 2 mg/kg B Wt. for three consecutive days was clinically and culturally found to be 100% effective in the treatment of naturally occurring *CCPP* in goats (Giadinis, *et al.,* 2008). In one case report, streptomycin-treated goats suffering from natural and experimental *CCPP* recovered on the third day of treatment and became completely immune to reinfection with Mccp (Rurangirwa and McGuire, 2012). The administration of long-acting oxytetracycline prevented morbidity and mortality that controlled further *CCPP* spread immediately (Ozdemir *et al.,* 2005). Danofloxacin was found to be highly effective in the treatment of clinical *CCPP* in goats. Commercially available vaccines such as Pulmovac and Capridoll (live) and *CCPP*V (killed) vaccines are produced in Turkey and Ethiopia, respectively. Caprivax is an inactivated *CCPP* vaccine

prepared from a Mccp strain by the Kenya Veterinary Vaccine Production Institute, Nairobi (Litamoi *et al.,* 1989). The inactivated Mycoplasma strain F38-saponin vaccine in natural *CCPP* cases showed 100% protection. In India, the use of attenuated live culture vaccine @ 0.2 ml intradermally at ear tip, is reported to provide immunity for 15 months. *CCPP* Vaccine is also prepared at the farm as Longley's formalized vaccine. Moreover in India IVRI has been preparing *CCPP* vaccine since 2000 (Srivastava, *et al.,* 2000).

Compliance with ethical standards
Conflict of interest

The authors declare that they have no conflict of interest.

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