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REVIEW ARTICLE

Current trends of canine parvoviral enteritis: Nigeria perspective

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Abstract

Background: Canine parvoviral enteritis (CPE) is currently considered one of the major leading causes of morbidity and mortality in dogs. Canine parvovirus (CPV-2) was first isolated in 1978, ever since then the virus has mutated to CPV-2a, CPV-2b and recently CPV-2c, which has made the control and eradication of disease seemingly impossible. The disease has been reported in several parts of the world including; USA, Canada, Australia, United Kingdom, Taiwan, and Tunisia, South Africa and Nigeria. The identification of the strains of CPV-2 that are currently circulating in the canine population is very essential for the understanding of viral evolution and the development of measures to control its spread. This review therefore, focuses on the current trends and antigenic variants of canine parvovirus type 2 (CPV-2) circulating in Nigeria.

Methods: Previous literatures were reviewed on the status of canine parvovirus type 2 in Nigeria. The emphasis was on the antigenic variants of CPV-2 circulating in Nigeria and strains of the virus in the vaccines, and out breaks of infections.

Results: Control and prevention of CPE has remained a global challenge, and relies mainly on extensive vaccination. Sequence analysis of CPV-2 has revealed the presence of the three antigenic variants in Nigeria. CPV-2c is now predominantly in Nigeria and as such with so many countries of the world, without corresponding vaccines with the variants. Hence understanding the antigenic variants of CPV-2 virus circulating within a geographical area is very essential in controlling the infection.

Conclusion: CPE is endemic in Nigeria and mainly infects dogs less than six months of age. The disease is of serious socio-economic importance to dog owners and breeders, as a number one killer disease of dogs. The three stains of the canine parvovirus type 2, (2a, 2b and 2c) exists in Nigeria, with predominantly 2c. The current vaccines mainly used in Nigeria are original CPV-2, 2a or 2b, and do not protect dogs against CPE due to 2c infections. We therefore, recommend that 2c be incorporated in CPV-2 vaccines presently used in Nigeria.

Keywords: Canine parvovirus; Antigenic variants; CPV-2; Vaccines; Dogs

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Introduction

Canine parvoviral enteritis (CPE) is a highly contagious disease caused by canine parvovirus (CPV-2), infecting domestic and wild carnivore (Mylonakis *et al,* 2016). The virus consists of a spherical capsid, which is composed of three proteins and a single stranded DNA molecule (Muzyczka and Berns, 2001). Canine parvovirus infection has been reported in many parts of the world, including Nigeria and has continued to be a serious threat to canine population despite the availability of vaccines (Carmichael, 2005). The disease was first reported in the USA in early 1978 (Meunier *et al.,* 1985), but the identification of the causative virus was first documented as CPV-2 in Canada in June 1978 (Appel *et al.,* 1979). However, comprehensive independent studies on the rate of CPV-2 molecular evolution has indicated that the virus must have emerged at least ten years earlier (Shackelton *et al.,* 2005), and thereafter fatal cases of enteric disease occurred with increasing frequency (Thomson, 1980).

The identification of the strains of CPV-2 that are currently circulating in the canine population is very essential for the understanding of viral evolution and the development of measures to control its spread (Pinto *et al.,* 2012). Control and prevention of canine parvoviral enteritis (CPE) has remained a global challenge, and relies mainly on extensive vaccination. Despite the aggressive vaccinations, and client education by veterinarians, CPE infection still poses great danger even among fully vaccinated dogs and leads to huge economic losses to pet owners and breeders especially among exotic breed dogs. Hence understanding the antigenic variants of CPV-2 virus circulating within a geographical area is very essential in controlling the infection (Truyen, 2006). This review therefore, focuses on the current trends and antigenic variants of canine parvovirus type 2 (CPV-2) circulating in Nigeria.

Classification of canine parvovirus type 2

The family Parvoviridae comprises two subfamilies, Parvovirinae and Densovirinae, infecting vertebrates and insects, respectively. Currently, five genera are included in the subfamily Parvovirinae, namely Parvovirus, Erythrovirus, Dependovirus, Amdovirus and Bocavirus. Canine parvovirus (CPV) belongs to genus Parvovirus, alongside with the unique species of Feline Panleukopenia virus (FPV), Mink Enteritis Virus (MEV) and Raccoon Parvovirus (RPV) (Tattersall *et al.,* 2005). CPV-2 is genetically and antigenically unrelated to Canine Minute Virus (CnMV), formerly known as canine parvovirus type1 (CPV-1), which is responsible for neonatal death in dogs and is now included in the genus Bocavirus together with Bovine Parvovirus and Human Bocavirus. CPV-1 was not associated with natural disease until 1992 (Tattersall *et al.,* 2005). CPV-1 has been reported in USA, Italy, and Germany and more recently in Japan (Prateli *et al.,* 1999; Mochizuki *et al.,* 2002). CPV-2 shows high rates of genomic substitutions similar to those of RNA viruses, with values of about 10-4 substitutions per site per year. The reported rate of substitution refers only to the VP2 gene. This high rate of evolution is similar to the rate of nucleotide substitution found with RNA viruses such as influenza virus A (Shackelton *et al.,* 2005).

Antigenicity and adaptations of canine parvovirus type 2

Canine parvovirus (CPV-2) was first isolated in 1978 (Appel *et al.,* 1979, Truyen, 2006) However further studies on the rate of CPV molecular evolution indicate that the virus likely emerged 10 years earlier (Shackelton *et al.,* 2005, Truyen 2006). The exact origin of CPV-2 is not known, although it is thought to have originated as a host range variant from FPLV or other Parvoviruses (Decaro and Buonavoglia, 2012). Since the original type CVP2 was discovered, several antigenic variants of CPV-2a, CPV-2b, and CPV-2c have replaced it entirely and have become distributed throughout the canine population worldwide (Decaro and Buonavoglia, 2012).

Phylogenetic analysis revealed that all CPV variants were descended from a single ancestor which emerged during the mid-1970s, was closely related to the long known feline

panleukopenia virus (FPV) which infects cats, minks and raccoons but not dogs or cultured dog cells (Truyen, 2006; Figure 1). The differences in DNA sequence between CPV and FPV isolates can be as little as 0.5% (Hueffer *et al.,* 2003). As CPV is a relatively new virus that continues to evolve and produce new antigenic types, the more predominant mutants are selected for by their ability to bind to the Transferrin Receptors (TfR) and by extending host range, in newer antigenic types, to include both dogs and cats (Truyen, 2006).

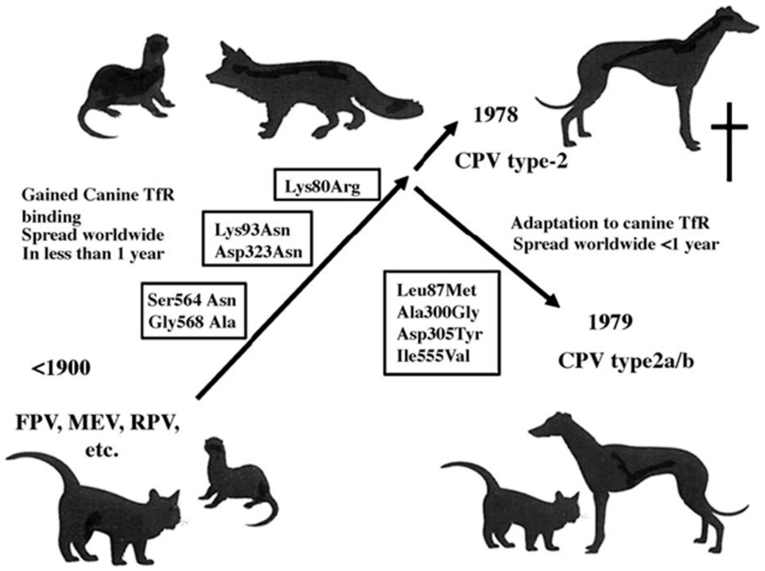

Figure 1: Evolution of Canine parvovirus from Feline panleukopenia virus. Adapted from Truyen, 2006.

Epidemiology of canine parvovirus type 2

Distribution and origin of canine parvovirus type 2 in Nigeria. Canine parvovirus emerged in1970s as a new infectious disease of puppies, characterized by either myocarditis or haemorrhagic gastroenteritis, which was observed worldwide. The incidence is higher in animal shelters, pet stores and breeding kennels than in free range dogs. The disease was first reported in 1977 in USA (Meunier *et al.,* 1985), and later the causative agent of the disease was first documented as CPV-2 in 1978 (Appel *et al.,* 1979). Ever since then, CPV-2 has been reported in several parts of the world, including Canada (Gagnon *et al.,* 2016), Australia (Meer *et al.,* 2007), United Kingdom (Decaro *et al.,* 2007; Decaro and Buonavoglia, 2012), Taiwan (Chiang *et al.,* 2016), and Belgium (Ntafis *et al.,* 2010).

In 1979 and 1980, an antigenic variant of CPV-2 was identified in several different countries using monoclonal antibodies (mAbs) and the variant was termed CPV-2a. In the mid-1980s, the virus underwent a further antigenic change, and the new variant was referred to as CPV2b (De Ybanez *et al.,* 1995). Currently, the antigenic

variants of CPV have completely replaced the original type 2 and are variously distributed in canine populations worldwide (Buonavoglia, 2001; Battilan *et al.,* 2002 Martin *et al.,* 2002; Sakulwira *et al.,* 2003). In 2000, a new variant was detected in Italy. The sequence analysis of the capsid protein-encoding gene revealed 2 amino acid changes in two isolates of CPV-2 collected from two dogs affected by severe haemorrhagic diarrhoea, strongly suggesting the existence of a new variant of CPV2c (Battilan *et al.,* 2002). In the recent time, the new variant CPV-2c has been detected in several countries. In an epidemiological survey, in Vietnam CPV-2c, was detected (Nakamura *et al.,* 2004). In2005,suchavariantwas also isolated from an outbreak of fatal gastroenteritis that occurred in a breeding kennel of Basset hounds located in Catalonia, Spain (Decaro *et al.,* 2006). The results of two different European epidemiological surveys (Decaro *et al.,* 2007, 2011b) showed that CPV-2c is now predominant in Italy, Germany and Spain and is also widely distributed in Portugal, France and Belgium, where CPV-2b or CPV-2a were more frequently detected. Sporadic isolation of CPV-2c has been obtained also from the United Kingdom, Greece and Bulgaria, where there was a higher frequency of CPV-2a/ 2b detection (Decaro *et al.,* 2007; Ntafis *et al.,* 2010; Filipov *et al.,* 2011).

Outside Europe, all three variants are well represented in Tunisia (Touihri *et al.,* 2009). Type 2b and 2c isolates predominate in North America (Hong *et al.,* 2007; Kapil *et al.,* 2007), whereas CPV-2c is more widespread in South America (Perez *et al.,* 2007; Calderon *et al.,* 2009) with the exception of Brazil, where all circulating strains were characterised as CPV-2a (Castro *et al.,* 2011). CPV-2a is the predominant variant in Asia (Kang *et al.,* 2008; Ohshima *et al.*, 2008; Nandi *et al.,* 2010) and Australia (Meers *et al.,* 2007), although few CPV-2c strains have been detected in India (Nandi *et al.,* 2010). The occurrence of CPV-2c was first reported 2010 in India (Nandi *et al.,* 2010), based on the sequence analysis of CPV-2b positive sample. Its presence in India supports the assumption that CPV-2c is reaching a worldwide distribution and provides new information to the understanding of the evolution of antigenic variants of CPV-2 (Nandi *et al.,* 2010).

In Nigeria, CPV-2 was first reported in 1985 in mongrel dogs (Kamalu, 1985). The occurrence of CPV 2 in Nigerian mongrel dogs raised questions as to the source of the infection for Nigerian dogs (Kamalu, 1985). Ever since then, the CPV-2 has been spreading in various parts of the country. Sequence analysis of the CPV-2 isolates from Jos, northern Nigeria, revealed that CPV-2a is the strain of the virus circulating in that region (Dogonyaro *et al.,* 2013). In a similar study CPV-2a antigenic strain was reported to be circulating in various part of Nigeria including Ibadan, Abuja and Makurdi (Apaa *et al.,* 2016). Further study in south western part of the country demonstrated the presence of all the three antigenic stains 2a, 2b and 2c in Nigeria (Fagbohun and Omobowale, 2018). This was the first to announce the presence of the latest antigenic variant of canine parvovirus 2c which evolved in the mid 2000 (Battlin *et al.,* 2002). Soon after the identification of CPV-2c in south western Nigeria, Ukwueze *et al.* (2020) detected the existence of predominantly 2c in south eastern part of Nigeria. Similarly, Shima *et al.* (2020) observed the existence of 2a and 2c in other seven states in Nigeria. In northern Nigeria, 2a and 2c was discovered to coexist, with predominantly 2c (Ogbu *et al.,* 2019). Presently the three variants of CPV-2 exist in Nigeria, with 2c predominantly isolated from infected animals.

Host range and susceptibility

CPV-2 isolates have been isolated from domestic dogs, wolves, and coyotes, as well as from other members of Canidae family (Evermann *et al.,* 1980; Mann *et al*., 1980; Parrish, 1990). CPV can replicate in both canine and feline cells in cultures, whereas FPV can replicate in feline but not canine cells (Truyen and Parrish, 1992). Studies with CPV–FPV recombinant genomes have shown that the canine host range is determined by the sequence between map units 59 and 73, within the overlapping coding sequence for VP1 and VP2 (Parrish and

Carmichael, 1986). FPV replicates efficiently *in vitro*, in feline cell lines, CPV can infect with the same efficiency cells of canine and feline origin. *In vivo*, FPV replicates in dogs in the thymus and bone marrow without being shed in the feces, and the original canine virus, CPV-2, does not replicate at all in cats. Conversely, both the type CPV-2a and CPV-2b variants have re-gained the ability to replicate *in vivo* in the feline host (Truyen, 2006).

Studies on the interactions of FPV and CPV with their cellular receptor, the transferring receptor type1, have revealed that FPV specifically binds the feline TfR, whereas CPV-2 and its variants can bind both the feline and the canine TfRs. Interestingly, the antigenic variants of CPV-2b in the canine and feline TfRs less efficiently than the CPV-2 which is the original type-2 (Palermo *et al.,* 2006). Cases of feline panleukopenia caused by CPV-2a or CPV-2b in wild and domestic felids have also been reported in different parts of the world (Truyen, 2006). More recently, cases of CPV-2c infection in cats were also observed in Italy (Decaro *et al.,* 2010a, 2011a).

Canine parvovirus has been reported in dogs of all ages, sexes and breeds (Castro *et al.,* 2007; Gombac *et al.,* 2008a). CPV commonly, infects 4–12 weeks old puppies that are prone to acquire the virus in concomitance with the wane of maternally derived antibody (MDA) (Greene and Decaro, 2012). Adults are thought to be resistant to CPV infection due to the age-reduced susceptibility and presence of specific immunity induced by vaccination or previous (often subclinical) infections. Although CPV infection is generally restricted to young animals but recently has become an issue in adult dogs. There are some scientific reports of the occurrence of parvoviruses in adult dogs, mostly associated with CPV-2c infection (Cavalli *et al.,* 2001; Decaro *et al.,* 2008a, 2009a). The cross breeds are less susceptible in comparison to pure breeds like Rottweiler, Doberman Pinchers, English Springer Spaniels and German Shepherd, the exception to this being Toy Poodles and Cocker Spaniels (Houston *et al.,* 1996). CPV affects only dogs, and cannot be transmitted to humans or other species. If a dog survives the first 4 days, they will usually recover rapidly and become immune to the virus for life. All infected dogs may not necessarily exhibit clinical manifestations but they may shed the virus in feces during the acute phase of enteric fever and show significant rise in the serum antibody titers (Stann *et al.,* 1984). Several species of wild carnivores, such as coyotes, raccoons, red foxes and wolves, are also susceptible to canine parvovirus infection, (Baker *et al.,* 1993; Truyen *et al.,* 1998). Canine parvovirus infection has also been reported in the bat eared fox, honey badger, cheetah, African wild cat and Siberian tiger (Steinel *et al.,* 2000).

Modes of transmission

Canine parvovirus CPV-2 is a highly contagious virus. It is mostly transmitted by direct and indirect contact with infected feces or contaminated surfaces (fomites) (soil, shoes, dog toys, hospital equipments etc.). The source of CPV infection to a susceptible animal is feco-oral route (Nandi and Kumar, 2010). The incubation period of CPV-2 in the field is 4-5 days, but the experimental infections are established within three days depending on immunity and dose of infection.

CPV-2 has been diagnosed wherever groups of dogs are found, for instance, kennels, pet shops, animal shelters, and play grounds (Black *et al,* 1979). It is easily transmitted via the hair or feet of infected dogs and also by contaminated objects such as cages or shoes. CPV is hardy and can remain in feces contaminated ground for 5 months or more if conditions are favourable. The feces of infected dogs contaminate places such as Veterinary hospitals, pet shops, boarding kennels and commercial breeding establishments. These contaminated premises serve as sources of infection to the susceptible canine population (Jacob *et al.,* 1980).

Transplacental transmission also occurs in non-immune, pregnant bitch. Due to widespread adult dog immunity, this is unlikely to occur. The majority of the pups that were born with

transplacental transmission normally die of cardiac failure. The virus localizes in the myocardial nuclei and is not shad. Dogs can be infected with CPV-2 by most parenteral routes (Parrish, 1990). Experimentally CPV-2 can also spread via injection of infectious material subcutaneously, intramuscularly or intravenously. This mode of transmission is used in research work, so that infective doses can be quantified or to bypass the initial lymphoid tissue phase of virus reproduction.

Clinical signs of canine parvoviral enteritis

The appearance of clinical signs of CPE infection generally surfaces within 3-7 days of initial infection, depending on the infectious dose of the virus (Aiello *et al.,* 2012). However, subclinical infection is also common and some dogs can be asymptomatic carriers of the virus (Johnson, 2014). Initially, nonspecific symptoms, such as fatigue, fever, dehydration, and inappetence will manifest. These symptoms will often develop into vomiting and haemorrhagic diarrhoea with a foul smelling or distinct odour, within 24-48 hours, after development of clinical signs (Aiello *et al.,* 2012; Johnson 2014). Intestinal loops can also become dilated and fluid-filled, causing abdominal pain (Aiello *et al.,* 2012). Animals with severe infections commonly exhibit signs of septic shock, characterized by a decrease in capillary refill time, tachycardia, and hypothermia (Aiello *et al.,* 2012). Endotoxin and tumor necrosis factor (TNF) are present in measurable quantities in the blood of infected puppies and a significant association exists between rising TNF activity and mortality (Otto *et al.,* 1997). Endotoxin and proinflammatory cytokines are potent mediators of the systemic inflammatory response and activators of the coagulation cascade. Rapid dehydration is a danger in disease progression, and affected dog may continue to vomit, and diarrhoeic until they die, usually 3 days after the manifestation of clinical signs. The severity of infection or manifestation of clinical signs cannot be used to distinguish between infecting strain. Although it has been speculated that CPV-2c is more pathogenic than CPV-2a and CPV-2b, however there is no evidence as CPV-2c causes similar clinical signs as the previously known strains, including mucoid or haemorrhagic diarrhoea, leukopenia and lymphopenia (Hong *et al.,* 2007; Kapil *et al.,* 2007). Some reports from other workers also indicate that CPV-2c may cause more severe clinical signs in adult dogs than CPV-2a and CPV-2b, whereas others suggest CPV-2c causes less severe disease with low motility rates in infected dogs (Joao *et al.,* 2008).

The morbidity and mortality vary according to the age of the animals, the severity of challenge and the presence of inter-current disease conditions. Puppies can die suddenly out of shock as early as 2 days into the illness (Stann *et al.,* 1984). The predisposing factors associated with the development of clinical parvovirus enteritis include stress factors such as weaning, overcrowding, parasite load, insufficient passive or active immunity, geographical area and the presence of co-infections with canine coronavirus (Goddard and Leiswits, 2010; Kalli *et al.,* 2010). Some of these factors are likely to increase the development of clinical canine parvoviral enteritis in dogs incubating the CPV-2 by increasing the mitotic activity of mucosal cells (Goddard and Leiswits, 2010).

The second form of CPV-2 is cardiac syndrome, or myocarditis form, which can affect mainly puppies under 3 months of age (Appel *et al.,* 1979). In an infected litter, 70% of the puppies will die of heart failure by 8 weeks of age and the remaining 30% will have pathological changes which may result in death in months or even years later. The most dramatic manifestation of CPV-2 myocarditis is the sudden death in young puppies of about 4 weeks of age (Mochizuki *et al.,* 1996). The collapsed dying puppy may have cold extremities, pale mucosae and show gasping respiration or terminal convulsions. Acute heart failure with respiratory distress occurs in puppies between 4 and 8 weeks of age. Sub-acute heart failure occurs in older puppies usually 8 weeks or more. There may be exercise intolerance, which usually manifests as tachyponea and dyspnoea. The abdomen may be swollen with hepatomegaly and ascitic fluid which is blood tinged (Carpenter

et al., 1980). There is tachycardia, sometimes with arrhythmias and a weak pulse. Most puppies die due to cardiogenic shock. However, if the animal survives it will suffer from chronic myocardial and circulatory complications (Hayes *et al.,* 1979; Robinson *et al.,* 1980). There is always no diarrhoea, because the virus multiplies rapidly in muscle cells of the immature heart.

Necropsy findings, will reveal thickening of the cardiac cell wall, haemorrhagic and watery intestinal contents, edema of abdominal and thoracic lymph nodes in dog that died of CPV-2 (Aiello *et al.,* 2012). In the intestine, lesions usually affect the jejunum and ileum but not the duodenum and colon. Affected segments may become flaccid with subserosal haemorrhage or congestion (Robinson *et al.,* 1980). The lumen of the intestine is often empty but may contain variable watery ingesta. The mucosal surface is often congested but devoid of exudates.

In cases of CPV-2 induced myocarditis, pale streaks can be observed in the heart muscle tissue. Gross lesions include cardiac enlargement with prominent dilatation of the left atrium and ventricle (Aiello *et al.,* 2012). The lungs often do not collapse when cut although white frothy fluid may be present in the trachea and bronchi. Evidence of pulmonary edema and passive congestion of the liver are often present, with variable degrees of ascites and pleural effusion. Some puppies may die from chronic decompensating left sided heart failure weeks or months after some of their litter mates died suddenly with acute myocarditis. Pulmonary hypertension and myocardial dilatation with scarring are often regarded as the cause of delayed death (Hayes *et al.,* 1979).

The histopathology of the small intestine will also reveal multifocal crypt necrosis and intranuclear inclusion bodies, and extensive depletion of lymphocytes in Peyer's patches, lymph nodes, spleen and thymus (Decaro and Buonavoglia, 2012). There may be occasional intranuclear eosinophilic inclusion bodies in intact crypt epithelial cells. The villi and lamina propria may collapse completely as a result of the loss of crypt epithelium and the failure to replace sloughed villous epithelial cells. These lesions may be extensive or diffuse. Loss of intestinal epithelium and absorptive surface area presumably results in diarrhoea caused by combined effects of maldigestion and malabsorption (Nandi and Kumar, 2010). Death may follow as a result of dehydration, electrolyte imbalance, endotoxic shock or secondary septicemia.

The regeneration of intestinal epithelial cells has been reported in some critical cases. The remaining intestinal crypts are elongated and lined by hyperplastic epithelium with a high mitotic index (Nandi and Kumar, 2010). The shortened villi are covered by immature epithelial cells and adjacent villi are often fused. Later in the disease, there is evidence of regenerative lymphoid hyperplasia.

Pathophysiology of canine parvoiral enteritis

After initial infection, the virus replicates in the lymphoid tissues of the oropharynx, mesentric lymph nodes and thymus (Decaro and Buonavoglia, 2012), then spreads through the blood stream (Johnson, 2014). CPV-2 attacks rapidly dividing tissues or cells of the intestinal crypt, lymphoid organs, and bone marrow (Aiello *et al.,* 2012; Johnson, 2014), but the virus can spread to all tissues (Pollock, 1982), including the brain (Elia *et al.,* 2007; Decaro *et al.,* 2009a). After penetrating through the intestinal cells, the virus replicates in gastro enteric associated lymphoid tissues and is disseminated by infected leukocytes to the germinal epithelium of the crypts of the small intestine, which impairs the absorptive capacity, cell turnover at the villi tips, and results in the onset of diarrhoea (Aiello *et al.,* 2012, Decaro and Buonavoglia, 2012). Within the bone marrow, the virus is responsible for the destruction of young cells of the immune system and then knocking out the body's defence mechanism. The virus causes most devastating effects in the gastro-intestinal tract. The normal intestine possesses little finger-like protrusions called ''villi''. These tiny fingers greatly increase the surface area available for the absorption of fluid and nutrients. To make the surface area

available for absorption, the villi possess ‘‘microvilli’’ which are microscopic protrusions. The cells of the villi are relatively short-lived and are readily replaced by new cells. The source of the new cells is the rapidly dividing area at the foot of the villi called the crypts of Lieberkuhn (McCandish *et al.,* 1981; Parrish, 1995). It is right at the crypt where the parvovirus strikes. Without new cells coming from the crypt, the villus becomes blunted and unable to absorb nutrients and diarrhoea results. The barrier separating the digestive bacteria from the blood stream breaks down. The diarrhoea becomes bloody and bacteria can enter the body causing widespread infection. The virus kills through one of the two ways, diarrhoea and vomiting lead to extreme fluid loss and dehydration until shock and death result. Loss of the intestinal barrier allows bacterial invasion of potentially the entire body.

Canine parvoviral enteritis (CPE) is characterized by a drop in white blood cell count due to the bone marrow infection. Infection of leukocytes, mainly circulating and tissue-associated lymphocytes, induces acute lymphopenia and neutropenia, which often results in the secondary infections (Pollock, 1982; Aiello *et al.,* 2012, Decaro and Buonavoglia, 2012). Anaerobic bacteria that are intestinal normal flora can then cross into the bloodstream, through a process known as translocation, causing bacteremia leading to sepsis. This can lead to a syndrome known as systemic inflammatory response syndrome (SIRS). SIRS lead to a range of complications such as hypercoagulability of the blood, endotoxemia and acute respiratory distress syndrome (ARDS). Bacterial myocarditis has also been reported secondarily to sepsis (Silverstein, 2003).

Dogs with CPE are at risk of intussusception, a condition where part of the intestine prolapses into another part (Ettinger and Feldman, 1995). Three to four days following infection, the virus is shed in the feces for up to three weeks, and the dog may remain an asymptomatic carrier and shed the virus periodically (Aiello *et al.,* 2012). The virus is usually deadlier if the host is concurrently infested with worms or other intestinal parasites. In 2-3 weeks old puppies, often lacking maternally derived antibodies (MDA), CPV2 can replicate in cardiac cells, without signs of enteritis, and result in fatal myocarditis (Aiello *et al.,* 2012, Decaro and Buonavoglia, 2012).

Treatment of canine parvoviral enteritis

Treatment of CPE infection in dogs focuses mainly on stabilizing fluid and electrolyte concentrations, preventing secondary bacterial infections, and controlling other clinical signs and symptoms (Johnson, 2014). Survival rate depends on how quickly CPV-2 is diagnosed, the age of the animal and institution of aggressive therapy. Treatment for severe cases that are not diagnosed early usually involves extensive hospitalization due to the severe dehydration and damage to the intestines and bone marrow. The severe dehydration is as a result of vomiting and diarrhoea, thus leading to alterations in fluid and electrolyte balance. In order to better manage fluid rehydration, infected dogs are often taken off of oral food and water, and placed on intravenous feeding until vomiting ceases (Johnson, 2014).

Intravenous (IV) crystalloid fluid therapy is preferable over subcutaneous fluid administration as the IV fluids will transport nutrients to the damaged enterocytes at a significantly faster rate (Johnson, 2014). Once the dog can maintain fluid, the IV fluids are gradually discontinued and very bland food slowly introduced. A puppy with mild clinical signs can recover in two or three days if the IV fluids are given as soon as clinical signs are noticed. If more severe, depending on treatment, puppies can remain sick from five days up to two weeks. Puppies admitted with severe hypovolemia need reestablishment of their circulating volume in 1–2 hours. As a rule, a balanced isotonic crystalloid solution (e.g., Lactated Ringers) is the fluid of choice for initial restoration of intravascular volume and rehydration, with a rate titrated to improve perfusion parameters, including capillary refill time, mucosal color, pulse character, and mean arterial pressure or lactate concentrations

(Anastasio *et al*., 2014). In dogs admitted without evidence of hypovolemic shock, hydration may be restored over 12–24 hours. The fluids should be typically a mixture of a sterile, balanced electrolyte solution, with an appropriate amount of B-complex vitamins, dextrose and potassium chloride. In addition, extra fluids should be given intravenously to achieve adequate rehydration; each time the puppy vomits or has diarrhoea of a significant quantity. The fluid requirements of each animal is determined by the animal's body weight, weight changes over time, degree of dehydration at presentation and surface area. A blood plasma transfusion from a donor dog that has already survived CPV is sometimes used to provide passive immunity to the sick dog. Some veterinarians keep these dogs on site, or have frozen serum available. There have been no controlled studies regarding this treatment (Macintire, 2008). Additionally, fresh frozen plasma and human albumin transfusions can help replace the extreme protein losses seen in severe cases and help assure adequate tissue healing. However, this is controversial with the availability of safer colloids such as Hetastarch, as it will also increase the colloid osmotic pressure without the ill effect of predisposing that canine patient to future transfusion reaction.

In addition to fluid treatments, patients are given a mixture of broad-spectrum antibiotics to prevent secondary infection, analgesics, and occasionally immune-boosting vitamins (Johnson, 2014). When the infection is caught early and with intensive treatment, the prognosis for affected dogs is good. The broad-spectrum antibiotics commonly used are ampicillin, chloramphenicol, erythromycin, gentamycin and metronidazole. Antiemetics used to control vomiting are chlorpromazine and metaclopromide.They are normally given at 0.5 mg/kg body weight intravenously at 8-hour interval. Cimetidine, omeprazole ranitidine, famotidine are drugs of choice used to correct gastric problems, while loperamide or bismuth subnitrate or other astringent preparations may be given to stop diarrhoea (Kramer *et al*., 1980). Analgesic medications can also be used to counteract the intestinal discomfort caused by frequent bouts of diarrhoea; however, the use of opioid analgesics can result in secondary ileus and decreased motility. A recent study has shown that puppies receiving early enteral nutrition via a nasoesophageal tube, showed marked clinical improvement, significant weight gain, as well as improved gut barrier function which could limit bacterial or endotoxin translocation compared to puppies that received nutrition orally (Mohr *et al*., 2003).

Prevention and control of canine parvoviral enteritis

The whole aim of prevention is to ensure that a puppy or dog remains healthy because CPV-2 is extremely virulent and contagious. There are three key factors involved in preventing the spread of CPV-2 infections namely; sanitation, isolation, and vaccination (Johnson, 2014). Under ideal/favourable conditions, CPV-2 can live in an environment for up to a year, and it has been found to be resistant to most common detergents and disinfectants, and extreme temperatures (Johnson, 2014) However, the virus can be killed by diluted bleach on hard surfaces (Ettinger and Feildman, 1995; Johnson, 2014). Dogs that recover successfully from CPV-2 will continue to shed the virus for a few days. Ongoing infection risk is primarily from fecal contamination of the environment due to the virus ability to survive many months in the environment. So, good hygienic practices in the kennels, including disinfection of all exposed surfaces and personnel are important, because of the extremely hardy nature of the virus in the environment. As CPV-2 is highly contagious, infected dogs should be hospitalized in an isolated ward to prevent the spread of the virus (Johnson, 2014). Isolation will also help protect the infected dog against contracting a secondary infection by minimizing their exposure to other susceptible dogs (Johnson, 2014).

Control of CPV-2 is a global challenge however; the most effective method of control is vaccination. Vaccines based on the original antigenic type CPV-2, have been shown to protect dogs against infection with the CPV-2a

and CPV-2b antigenic types (Yule *et al*., 1997), and certain vaccines based on FPLV have been shown to protect from being infected with CPV-2b (Chalmers *et al*., 1999). The ideal vaccines for CPV-2 should contain the latest antigenic types of the virus, as this implies the most complete protection, provided the new vaccines are as immunogenic as the old ones (Truyen, 2006). Effective immunization is essential for the protection of the individual pet and the decrease of the population of susceptible animals in a region, thus promoting "herd immunity" (Day *et al*., 2016). Puppies are generally vaccinated in a series of doses, extending from the earliest time that the immunity derived from the mother wears off until after that passive immunity is definitely gone (Oh *et al*., 2006). The initial puppy vaccination series starts normally at 6–8 weeks of age, and then every 2–4 weeks until 16 weeks of age or older (Day *et al*., 2016). If the dog is admitted for the initial vaccinations after the age of 16 weeks, two doses 2–4 weeks apart are generally recommended, even though one dose of MLV is very likely protective (Schultz *et al*., 2010). According to the recently revised guidelines for the vaccinations of dogs and cats endorsed by the World Small Animal Veterinary Association, the first booster vaccine after the end of the initial series is now recommended to be delivered at any time between 6 and 12 months of age; however, 6 months of age is a convenient timing for the puppies that have completed their initial series at the age of 4 months. Thereafter, vaccinations for CPV (similar to other canine core vaccines) are given no more often than every 3 years (Day *et al*., 2016). There are both inactivated and attenuated vaccines available for use against CPV2 (Decaro and Buonavoglia, 2012). Modified live vaccines (MLVs) are currently used worldwide affording prolonged (7 years or longer) immunity that would confer protection against both disease and infection (Twarks and Dodds, 2000; Abdelmagid *et al*., 2004; Mouzin *et al*., 2004; Schultz *et al*., 2010), inactivated vaccines only provide short-term immunity (Decaro and Buonavoglia, 2012). These vaccines are made using either the original type CPV-2 or the CPV-2 variants. However, there are concerns about the effectiveness of CPV-2 based vaccines against variant CPV2 strains (Decaro and Buonavoglia, 2012). In most CPV-2c outbreaks reported in adult dogs so far, the animals had undergone the full vaccination schedules including a booster vaccination on yearly basis (Decaro *et al*., 2008, 2009). CPV-2 variant outbreaks involving younger dogs that have completed their vaccination protocol scheduled for the first year of life have been reported (Kapil *et al*., 2007; Perez *et al*., 2007; Calderon *et al*., 2009; Ntafis *et al*., 2010; Castro *et al*., 2011; Filipov *et al*., 2011). Protections elicited by CPV-2 based vaccines against the field variants are still questionable, as the current opinions are highly divergent. Many authors have suggested that the old type-2 based vaccines are still protective against the variants currently circulating in the field. On the other hand, other researchers believe that the immunity induced by CPV-2 vaccines is effective against the homologous (vaccine) virus but significantly lower against the variants, thus allowing an aggressive strain to cause infection and even mortality in vaccinated dogs. It has been shown that there is a one-way cross-reactivity between the antigenic variants and the original CPV-2.

Several authors have reported high mortality rate of CPE in Nigeria, which likely due to presence of 2c, because the sequence analysis of the vaccines mainly used in Nigeria have been shown to either contain original CPV-2, 2a or 2b strain (Adejumobi *et al*., 2017; Ukwueze *et al*., 2018; Fagbohun and Omobowale, 2018; Ukwueze *et al*., 2020). It has been widely stated or opined that for effective control of CPV-2, the vaccines used should contain the latest antigenic variant of the virus circulating the geographical area (Truyen, 2006). Previous study (Ukwueze *et al*., 2020) reported outbreak of the CPV-2c cases in 14 dogs and 11 dogs died in Nigeria even after vaccination. This may likely be due to non-protective effects of the vaccines used, rather than blockage of maternally derived antibody. Recent reports suggest that CPV-2 vaccines does not show cross protection immunity (Decaro and Buonavoglia, 2012; Ukwueze *et al*., 2020)

Beside the available vaccines (live attenuated and inactivated vaccines) new generation vaccines namely recombinant vaccine, peptide vaccine and DNA vaccine are in different stages of development and offer hope for better management of canine diseases. However new generation vaccines have not been issued to be used in field conditions (Nandi and Kumar, 2010). Again, the presence of maternal antibodies often interferes with active immunization with live attenuated vaccine and there always exists a window of susceptibility in spite of following proper immunization regimen.

Conclusion

CPE infection is endemic in Nigeria and mainly infects dogs less than six months of age. The disease is of serious socio-economic importance to dog owners and breeders, as a number one killer disease of dogs. The three stains of the canine parvovirus type 2, (2a, 2b and 2c) exists in Nigeria, with predominantly 2c. The current vaccines mainly used in Nigeria are original CPV-2, 2a or 2b, and do not protect dogs against CPE due to 2c infections. We therefore, recommend that 2c be incorporated in CPV-2 vaccines presently used in Nigeria.

Competing Interest

The authors declare that they have no competing interests.

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