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A Review On Botulism And Its Importance In Human And Animal Populations

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Abstract: Botulism is a rare but serious neuroparalytic disease of both human and animal caused by absorption of performed neurotoxin produced by *Clostridium botulinum,* which is rod-shaped, gram positive, motile, obligate anaerobic and spore forming clostridia specie. Temperature, pH, water activity, redox potential, food preservatives, and competing microorganisms limit the growth of *Clostridium botulinum* in food. *Clostridium botulinum* is an alimentary bacterium can produces heat resistant spores that able to poisoning the food ingested and release toxins in the intestinal tract after germination which results botulism. The spores are common in the environment especially in soil, sediments and water. *C. botulinum* also produces eight different types of poisons neurotoxins having same therapeutic value and inactivated by heating at 85°c for five minutes. The potent *botulotoxin* binds to nerve endings where block the release of acetylcholine to motor neurons, leading to typical sign progressive flaccid paralysis. Rapid treatment by antitoxin is essential, unless death is most likely to occur due to respiratory failure. Sporadic as well as outbreaks could occur, cause significant economical loses. In areas where botulism is prevalent, vaccines may be used in animals. Proper boiling and heating of home canned foods before consumption and vaccination will reduce botulism intoxication. Proper disposal of contaminated materials, avoiding eating of expired and bulged canned food items, and burning or burying of carcasses should be practiced as preventive measures.
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1. Introduction

Botulism is a serious neuroparalytic disease of humans, all warm-blooded animals, birds and some fishes. It is also a toxic infection, usually a food borne, and a rare but severe neuroparalytic disease resulting from the action of a potent toxin produced by the rod-shaped, gram positive, motile, spore forming and anaerobic bacterium called *Clostridium botulinum*. The disease is caused by absorption of preformed toxin produced by *Clostridium botulinum* and other *botulinum* toxin–producing clostridia species. *C. botulinum* is an alimentary bacterium form spores under anaerobic conditions. Its spores can survive for almost 30 years and commonly found in the environment, especially in soil, sediments and waters, but can germinate and grow only under specific conditions. *C. botulinum* pathogens occur worldwide and are associated with soil, decaying and rotting vegetative material or cadavers. It produces eight different types of neurotoxins, such as A, B, C α, Cβ, D, E, F and G (Galey *et al.,* 2000; Bohnel and Gessler, 2010). Sporadic cases as well as outbreaks occur, and often affect the whole livestock when there is a common source of contamination, causing significant economical losses (CFSPH, 2010).

In humans botulism is typically caused when food is improperly preserved and this is called food borne botulism which is the most common type in human beings. The intoxication is often due to failure in the heating process during food processing. If the food is insufficiently pasteurized or heat treated the spores will survive and production of toxins occurs in the food (Critchley, 1991; Lindstrol *et al.*, 2010).

After ingestion of *C. botulinum* spores they germinate in the intestinal tract of humans where they release toxins and called infant botulism. Toxicoinfectious botulism is also well documented in human infants (Bartram and Singer 2004). The infant intestinal tract lacks natural defense systems, which is normally developed in most adults. Wound botulism in humans is another type of botulism which occurs when open wounds or injured tissues contaminated with *C. botulinum* spores that proliferate and produce the toxin locally (CFSPH, 2010).

The *botulotoxin* is the most potent toxin known. Toxin binds to nerve endings where they block the release of acetylcholine to motor neurons, leading to

progressive flaccid paralysis in both humans and animals. If there is no rapid treatment, death is most likely to occur due to paralysis of the respiratory muscles (Mc Vey *et al.,* 2013).

The ability of *C. botulinum* to cause food poisoning in humans is directly related to the production of heat-resistant spores. In many cases, it is impractical or undesirable to treat a food product in a manner to eliminate all *C. botulinum* spores. As a result, most control methods focus on the inhibition of growth and toxin production. The main limiting factors for growth of *C. botulinum* and toxin production in foods are: temperature, pH, water activity, redox potential, food preservatives, oxygen level and competing microorganisms. All of these factors are interrelated and so, changing in one factor influences the effect of other factors (Kim, and Foegeding, 1992; Johnson, 2000).

Botulism in animals represents a serious environmental and economic concern because of the high mortality observed during the outbreaks. In cattle, Botulism is caused mostly by the ingestion of the preformed BoNT type B, C and D. BoNT C and D are mostly associated with the ingestion of carcasses and broiler litter (Dirksen *et al*. 2006). BoNT B is mostly connected with rotten vegetation or feedstuff (Rings, 2004; Hogg *et al*. 2008).

All forms of botulism manifest essentially the same distinct clinical syndrome of symmetrical cranial nerve paralysis that may be followed by descending, symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory compromise and death. Rapid diagnosis, provision of intensive care, and administration of botulinum antitoxin are the cornerstones of treatment. Antitoxin is available exclusively from public health authorities, who immediately investigate potential sources to prevent additional illness (Shapiro *et al.,* 1997). In areas where botulism is prevalent, vaccines may be used in animals including horses, cattle, sheep, goats, mink and birds (CFSPH, 2010).

Therefore, the main objectives of this seminar paper are to review imperative points on Botulism.

2. Literature Review

2.1. General points

The genus *clostridium* contains several species that are found in many places in the environment, mostly on the soil. The species of clostridia are all characterized by being gram positive, spore-forming anaerobic producing extracellular toxins. Their size varies between 0.2-4µm and 2-20µm, and their ability to form spores is crucial to withstand the intestinal environment. Botulism is not caused by the bacterium *Clostridium botulinum*, but rather by the toxins that it produces. *Botulinum* toxin is produced only after the spores germinate, when the organism is actively growing and multiplying. *C. botulinum* also a member of family of lethal pathogens those are all capable of causing rapid, severe sickness and death, because of productions of most potent biotoxins. Tetanus, blackleg, and malignant edema are other diseases caused by members of the *Clostridium* genus (McVey *et al*., 2013; Radostits *et al*. 2006).

2.2. Etiology

Botulism is caused by absorption of *botulinum* neurotoxin (BoNTs) produced by anaerobic, spore-forming, motile bacteria called *clostridium botulinum* during vegetative growth. The most common causes of Botulism in animals are types C and D, but in humans usually caused by toxin types A, B and E. In rare cases by types F and G are also described (Galey *et al*. 2000; CFSPH, 2010). Type G was identified in 1970 but has not been determined as a cause of botulism in humans or animals (FDA 2012). The strains of *C. botulinum,* each distinguished by its production of a serologically distinct botulinum type (CDC 2014).

The species *Clostridium botulinum* and some strains of *Clostridium baratii* and *Clostridium butyricum* are BoNT-producing clostridia, but *C. botulinum* is mostly responsible for causing botulism (Nakamura *et al*., 2010).

On the basis of their genotypic, phenotypic, and biochemical characteristics, these strains are divided into 6 groups: *C. botulinum* (group's I-IV), *C. butyricum*, and *C. baratii*. Groups I and II, *C. butyricum,* and *C. baratii* are mainly associated with human botulism, whereas group III organisms are mainly responsible for animal botulism. Group IV organisms, also known as *Clostridium argentinense,* are associated with wound botulism. Group I and II organisms are capable of producing type A, B, E, and F toxins; group III organisms can produce type C, D, and their mosaic C/D and D/C toxins (Takeda *et al*., 2005 and 2006; Nakamura *et al*., 2010). Group IV*, C. butyricum*, and *C. baratii* produce type G, E, and F toxins, respectively (Santos *et al*., 1998; Demedici *et al*., 2009).

C. botulinum is motile by peritrichous flagella which are arranged singly, in pairs, or in small chains. It is also rod shaped with round extremities and is about 0.8-1µm wide and 4-6µm long. C. botulinum develops into ovoid spore that is highly resistant in the environment. It requires an oxygen free environment for its growth because of it is an obligate anaerobic bacterium and Optimum temperature ranges between 16-40^{0}c (approximately 25^{0}c) with some exceptions between strains. The optimum for toxin production ranges from 25^{0}c-42^{0}c and the bacteria prefer slightly alkaline environment (PH 7-7.6) (Akakpo and Bonfoh. 2010). Type D strains can produce toxin in carrion at a temperature as low as 9^{o}c, whereas a type C strain

failed almost completely to do it at 16^0c (Ortiz and Smith, 1994).

C.botulinum is classified as a single species, but it is divided into four phenotypic groups (Group I-IV), based on the ability to digest complex proteins. Group I have proteolytic characteristics and produces type A, B, and F toxins, but Group II have Non-proteolytic characteristics and produces type B, E, and F toxins. Group III strians produces type, Cα, Cβ and D. group-IV contains only strains producing BoNT serotype G. *C. botulinum* strains play a vital role in the natural carbon recycling process, growing in decaying organic matter and producing high levels of BoNTs (Lund and Peck, 2000; EFSA, 2005; Sykes, 2014).

C. botulinum spores can survive for almost 30 years and germinate under warm and humid conditions. The ability of *C. botulinum* to cause food poisoning in humans is directly related to the production of resistant spores that survive preservation methods that kill non-sporulating organisms. The heat resistance of spores varies from type to type and even from strain to strain within each type; although some strains will not survive at 80 ^{0}C, spores of many strains require temperatures above boiling to ensure destruction. The thermal resistance of spores also increases with higher pH and lower salt content of the medium in which the spores are suspended (Kim and Foegeding, 1992).

Spores can have resistance to alcohol, quaternary ammonium, phenol compounds and ultraviolet rays. But the vegetative form has low resistance to the environment. Spores are not resistant to gamma radiation, formaldehyde, ethylene, propylene, and heat. Spores are found more heat resistant at low water activity and natural pH values, and more sensitive at low pH values. proteolytic spores are inactivated at 121^0c for 3 minutes, and non-proteolytic spores inactivated by 90^0c after 10 minutes (EFSA,2005).

2.3. Epidemiology

2.3.1. Occurrence

Botulism has no geographical limitations, sporadic outbreaks occurring in most countries. The source of exposure to toxin and the risk for disease differ between regions because of differences in food storage, feeding, and management practices. Outbreaks associated with ingestion of toxin in conserved feeds are more common in the northern states of the USA and Europe, whereas outbreaks in animals on pasture are reported primarily from South Africa, Australia, and the Gulf coast area of the USA. The disease usually occurs in a number of animals at one time and has a high case fatality rate (Radostits *et al*., 2006).

C. botulinum pathogens occur worldwide and are associated with soil, decaying and rotting vegetative material or cadavers. The distribution of the organism is not homogeneous, as a result of environmental factors influence where botulism is seen. For example, the disease in southern African cattle is common because of phosphorus-poor soils. The main habitat of clostridia is the soil but they are also found in sewage, rivers, lakes, sea water, fresh meat, and fish (Haagsma, 1991).

The incidence rate of botulism in the US is low due to increasing education and awareness of proper storage and handling of foods. There were 121 reported cases of botulism in 2009, of which 11 were food borne, 84 infant, 23 wound, and 3 of unknown or other etiology (CDC, 2014). In 2011, a total of 140 confirmed cases of botulism were reported to the CDC. Of these, 20 were foodborne, 102 infant, 13 wound, and 5 of unknown or other etiology (CDC, 2014). While fewer cases of foodborne illness are caused by *C. botulinum* per year than by Salmonella, the death rate from botulism is relatively high, 17.3 percent, compared to 0.5 percent for *Salmonella* (Scallan *et al*., 2011).

Since the recognition of infant botulism in 1976, cases have been identified with increasing frequency. In the United States, 1442 cases were reported to CDC from 46 states between 1976 and 1996. Type A accounted for 46.5% of these cases and type B for 51.9%. Since reporting began to stabilize in 1980, the average annual incidence of reported infant botulism in the United States has been approximately 1.9/100,000 live births. Since 1976, 47.2% of all infant botulism cases have been reported from California. Between 1976 and 1994, the incidence of infant botulism was highest in Delaware, Hawaii, Utah, and California (9.0, 8.8, 6.3 and 5.7 per 100,000 live births, respectively). Affected infants are also more commonly breast-fed, and breast-feeding is associated with an older age at onset in type B cases (Long, 1985).

2.3.2. Species affected

Preformed toxins in a variety of sources including decaying vegetable matter (e.g., grass, hay, haylage, grain, spoiled silage), meat and fish, carcasses, invertebrates and contaminated water can cause botulism in animals (CFSAN; 2009). Susceptible animals are herbivores such as horses, mules, sheep, cattle, and goats including, birds, fish, fur animals (fox, otter, and mink) and humans also susceptible. Guinea-pig and mouse are highly susceptible and used as laboratory animals for laboratory diagnosis (Akakpo and Bonfoh, 2010). Carnivores usually feed the toxins in contaminated meat or fish, or ingest the toxins in carcasses (possibly including iguanas) or decaying, high protein garbage. But in pigs and domestic carnivores, botulism is rear, due to its feeding habits and adaptive response to a carnivorous lifestyle (Sykes, 2014).

Nutritional factors may lead to botulism in ruminants. Phosphorus deficient cattle may develop pica which leads to chew on cadavers and bones in order to balance their mineral deficiency, putting them at high risk of BoNT ingestion (Braun *et al.,* 2005; Radostits *et al.,* 2006); a gram of dried flesh may have enough botulinum toxins to kill a cow and Similar cases occurred in Australia, where protein-deficient sheep sometimes eat the carcasses of rabbits and other small animals. Herbivores also become ill when they feed the toxin in forage such as hay or insufficiently acidified silage. These feeds may be contaminated by the toxin-containing carcasses of birds and mammals, or from other sources of *C. botulinum*. The feeding of poultry litter containing type C spores has been linked to some outbreaks in ruminants (Braun *et al*., 2005; Dirksen *et al*., 2006)

Birds can ingest *botulinum* toxins in maggots that have fed on contaminated carcasses or invertebrates from water with decaying vegetation. Fish have been suggested as the source of the toxin in some outbreaks among birds. Contaminated feed can also result in cases in poultry. In addition, botulism has been described in animals that drank water contaminated by a carcass or other source of toxin (CFSPH, 2010).

The toxic infectious form of botulism in animals corresponds to the wound and intestinal forms in humans. Similarly to human infants, botulism in foals (the shaker foal syndrome) seems to be caused by the growth of *C. botulinum* in the gastrointestinal tract and has been suspected in foals suffering from equine grass sickness (Wylie and Proudman, 2009). Rare cases of wound botulism have been seen in some species such as horses. Botulism is more frequent in horses than any other herbivore. Toxicoinfectious botulism is also seen in chickens, when broilers are intensively reared on litter (Bartram and Singer 2004).

Botulism is not contagious, but it can be transmitted between animals by predation or cannibalism. Contaminated foods usually contain spores as well as the toxin. Spores that are passing through the gastrointestinal tract may germinate and grow if the animal dies. This can perpetuate the cycle, and may result in large outbreaks. Outbreaks of botulism can also contaminate the environment with spores; making future outbreaks more likely. Cold blooded animals are not receptive for botulism (Akakpo and Bonfoh, 2010).

2.3.3. Source of infection

Spores are found in soil worldwide, marine sediments, some agricultural products (e.g., honey), the intestinal tracts of some animals including fish, and household dust. Botulinum toxin retains much of its activity in untreated water and beverages for up to 70 days; water treatment processes inactivate the toxin (Heyman, 2008). Growth of *C. botulinum* and production of toxin is favored in canned food products with low-acid, low-salt, low-sugar, and low oxygen content. Home-canned vegetables fruit and fish products are now the most common sources of botulism. Modern industrial canning was developed expressly for killing *C. botulinum* spores (Soble, and Jeremy, 2005).

Most incidents of botulism are associated with the ingestion of preformed toxin (forage botulism). Toxin in feeds may result from the primary growth of C. botulinum in the feed or from the contamination of the feed with toxin containing carrion (carrion-associated botulism). Less common sources are growth with toxin production in wounds (wound botulism) or growth and toxin production in the alimentary tract (toxic infectious botulism) (Radostits *et al*., 2006).

Infant botulism occurs when an infant ingests spores of *C. botulinum* which in turn colonize the intestinal tract and produce toxin. In a prototypical case, type B organisms, but no toxin, were isolated from honey fed to an infant with infant botulism whose fecal specimens contained type B organisms and toxin. Family members who eat some of the same honey did not become ill (Arnon, 1992).

Spores of *C. botulinum* are common in marsh soil and can persist there for and animals living in marsh areas ingest spores frequently (Reed & Rocke, 1992). Decaying animal material provides a suitable substrate for *C. botulinum* growth, vertebrate carcasses being of particular importance. When an animal containing *C. botulinum* spores dies, putrefaction, invasion of tissues by C. botulinum from the gut, and associated toxin production occurs (Smith & Turner, 1987).

The larvae of sarcophagus fly Sarcophagi spp., feeding on the carcasses, are not affected by the toxins but effectively act to concentrate the toxin. Ingestion of a single toxigenic maggot could be lethal and their carcasses become substrates for the generation of further toxins and more maggots, thus perpetuating the cycle. Despite its microbiology being well understood, management of the disease still primarily consists of carcass collection during epizootics rather than any form of preventative management (Wobeser, 1997).

2.3.4. Risk factors

Animal risk factors**:** Botulism in animals represents a serious environmental and economic concern because of the high mortality observed during the outbreaks. It is most common in birds particularly, the domestic chicken and wild waterfowl. Cattle, sheep, and horses are susceptible while pigs, dogs, and cats appear to be resistance. The horse appears to be particularly susceptible to type B toxins. Cattle and sheep are usually affected by type C and D (Radostits *et al*. 2006).

Environmental risk factors: Botulism in a range of animals has seasonal distribution. Outbreaks most likely occur during drought period when feed is sparse, phosphorous intake is low and decaying flesh is very high. Silage associated botulism with the feeding of silage. The variation that occurs in the geographical distribution of the various types and in carrion versus non-carrion associated botulism is an important factor when considering prophylactic vaccination programs (Radostits *et al*. 2006).

2.3.5. Transmission

Botulism usually occurs when people or animals ingest the toxins in food or water, or when the spores germinate in anaerobic tissues and produce toxins as they grow. Botulinum toxin does not pass through intact skin, but it can cross mucous membranes and broken skin. Laboratory accidents can cause botulism by inhalation of the aerosolized toxin or other means, and bioterrorism is a possibility. Animal, as well as human botulism, the primary contamination route is the ingestion (absorption) of preformed toxins in foods or feeds. Raw material, such as grass, hay, rotting vegetation, and slaughterhouse waste, as well as decay of vertebrate carcasses, invertebrates, and sewage may support BoNT producing clostridia growth and toxin production (Smart *et al*., 1987).

Animals may directly ingest decaying organic matter containing toxin, or they may ingest toxins through the consumption of zooplankton or invertebrates, such as larvae, that have consumed toxic material. Typically, type C and D toxins are associated with carrion of birds or small animals that have contaminated water, feed, or the environment, while non-carrion-associated botulism is caused by type A and B toxins (Sharpe *et al* 2008; Ostrowski *et al*., 2012).

A second form of animal botulism is associated with the absorption of BoNTs produced *in vivo* in the intestinal tract. This form of botulism, seen in chickens and horses, can be categorized as a toxicoinfection. Bohnel and colleagues describe a toxicoinfection in cattle, referred to as ‘‘visceral botulism. This form of animal botulism is hypothesized to occur when C. botulinum colonizes the lower section of the intestine. BoNT is formed and partially absorbed by mucous membrane, and the rest is excreted with the feces. Excretion of feces containing BoNTs by animals that do not show any clinical symptoms of acute paralysis may demonstrate the production of toxins in the lower sections of intestines where only a low amount is absorbed, in contrast to the proximal parts of the intestinal tract in which toxins are highly absorbed (Bohnel *et al*., 2001).

A third form of animal botulism is caused by the germination and production of BoNTs by C. *botulinum* spores in infected wounds. The last two forms are often referred to as toxicoinfectious form botulism (Liguori *et al*. 2008).

The CDC categorizes human botulism cases into four transmission categories: foodborne, infant, wound, and other (CDC, 2014). Foodborne botulism results from the ingestion of preformed botulinum toxin in food. The toxin can be found in food that has not been properly cooked, processed, handled, or canned and is often present in canned food such as vegetables, meat, and seafood products. Infant botulism occurs when infants (persons less than one year of age) ingest *C. botulinum* spores that then germinate and produce the botulinum toxin in the intestines. Honey is a common dietary source of *C. botulinum* spores; infants should never be fed honey (FDA, 2012).

Wound botulism results when *C. botulinum* infects a wound and produces the toxin, which is then carried throughout the rest of the body via the bloodstream. Adult intestinal toxemia/colonization (which occurs in the same way as infant botulism), and iatrogenic botulism (an accidental overdose of the toxin injection) are also included in the classification, but no secondary person-to-person transmission has been recorded (CDC, 2014)

2.3.6. Zoonotic implications

Botulism cannot be directly transmitted from diseased animal to humans who handle them. But the potential sources of contamination are faces, tissues, and body fluids from animals with botulism. The meat and the milk from cattle that have botulism should not be used for human consumption (Radostits et al., 2006).

Botulism in humans is usually the result of eating improperly home-canned foods and is most often caused by type A or type B botulinum toxin. There have been several human cases of type E botulism in North America from eating improperly smoked or cooked fish or marine products. Type C botulism has not been associated with disease in humans, although several outbreaks have been reported in captive primates. Through cooking destroys botulinum toxin in food. Foodborne botulism cannot be spread from person to person. Although it is one of the least common of the foodborne diseases, anyone is susceptible to *C. botulinum* illness (as foodborne intoxication) even with the ingestion of only a small amount of toxin present in contaminated food. Immuno-compromised individuals, young children and elderly individuals may suffer from more serious symptoms (CDC, 2014).

2.4. The *Botulinum* toxin

C. botulinum produces eight different types of neurotoxins: A, B, C α, Cβ, D, E, F and G (Bohnel and Gessler, 2010). Botulinum neurotoxins are the most

poisonous poison, and colorless, odorless and presumably tasteless. The toxins are inactivated by heating higher than 85°C for five minutes (McVey *et al*., 2013).

The *botulinum* toxins consist of two polypeptide chains, a heavy chain and a light chain linked by disulphide bond. The light chain includes zinc peptidase activity. The heavy chain has a translocation domain being responsible for the formation of a spore through which the light chains passes and a binding domain for binding to nerve cells. Although the toxin types have very similar and chemical properties, they differ greatly in toxicity for different animal species. All eight types of *botulinum* neurotoxins (BoNT) are zinc endopeptidases with same hydrolytic activity on docking proteins required by neurotransmitter containing vesicles to fuse with the presynaptic membrane. Blockage of the release of neurotransmitters (acetylcholine) due to hydrolysis and this is the same result for all the toxin types. What distinguishes the toxin types is that they hydrolyze different docking proteins. That means C. *botulinum* type A and E hydrolyze SNAP-25 (synaptosomal-associated protein 25). Toxin types B, D, F, and G hydrolyze VAMP (vesicle associated membrane protein, also known as synaptobrevin). Type C hydrolyzes SNAP-25 and a protein on the target membrane, syntaxin. A hydrolyzed synapse requires weeks to months to regenerate (McVEY *et al.*, 2013; Sykes, 2014).

One of the most fascinating aspects on *C. botulinum* in recent years has been development of the most potent toxin into a molecule of significant therapeutic utility. Several pharmaceutical preparations of botulinum toxins for the treatment of human diseases in ophthalmology, neurology and dermatology are marketed with the trade names *Botox*®, *Dysport*® and *Xeomin*® (based on *botulinum* neurotoxin A), and *Myoblock*® / *Neuroblock*® (based on *botulinum* neurotoxin B). Except *Xeomin*, which is practically devoid of complexing proteins the other commercial formulations of botulinum toxins include, besides the neurotoxin, other bacterial complexing haemagglutinins and nonhaemagglutinin proteins as well. Several additional substances such as albumin, sucrose, lactose are included in these preparations for drug stabilization and facilitation of administration by intramuscular injection. *Botox*® is Avery known cosmetic product to eliminating wrinkles and smooth out the skin. The most side effects include temporary posies, headache, flu, nausea, and facial pain swelling (Ranoux et *al.,* 2002; Sampaio *et al*., 2004; Dressler and Beneck, 2007).

The US FDA has approved use of these preparations in cervical dystonia, blepharospasm, spasmodic, torticollis, strabismus and glabellar frown lines. In recent years type A botulinum toxin has been used in the treatment of spasmodic torticollis. This muscle disorder is characterized by the neck muscles contracting involuntarily causing abnormal posture of the head and neck. Controlled amounts of the toxin are injected directly in to two or more neck muscles. Due to the blockage of transmission of acetylcholine, the muscles relax. After repeated treatments, the muscle tension will eventually return to its normal level. Botulinum toxin is concluded to be the most effective available therapy for spasmodic *torticollis* (Granum, 2007).

Botulinum toxin is a category A biological agent, and it has been extensively weaponized by governmental military programs (Bermudoz, 2001) and was deployed by a terrorist group. So, BoNTs and BoNT-producing clostridia create an additional concern because of their potential use as biological weapons and bioterrorism (Dembek, 2007; CFSPH, 2010**).** Due to their absolute neurospecificity these neurotoxins do not react with any substrates in the presynaptic motor neurons, and extremely toxic. The two most likely mechanisms for use of botulinum toxin as a terrorist weapon include deliberate contamination of food or beverages or via an aerosol release (Villar *et al*., 2006).

2.5. Pathogenicity and resistance

C. botulinum is an alimentary bacterium where botulism can be caused by ingestion of preformed toxin. The toxins are the most potent accordingly one milligram contains 4800000 MLD (minimal lethal doses) for guinea pigs. The MLD (minimal lethal doses) of type A toxin in mice is 1.2ng per 1gram of body weight intraperitoneal inoculation (Sykes, 2014). The lethal dose for a person by the oral route is estimated at 30ng, by the inhalational route 0.80 to 0.90 µg, and by the intravenous route 0.09 to 0.15 µg. assuming an average weight of 70 kg each of 5.6 billion people, only 39.2 g of pure BoNT would be sufficient to eradicate humankind (Peck, 2006).

Resistance to botulism depends on circulating antitoxins. Some animals such as turkey, vultures; apparently acquire immunity through repeated sub lethal exposure. In botulism outbreaks, toxin is released in the tissue of the organism. Animals are protected against the disease if antitoxins produced by their immune system after initial exposure to the specific toxin type. It is necessary to select antitoxins of the serotypes that are present in the particular region for successful treatment or vaccination (Dwight *et al*., 2004).

2.6. Pathogenesis

BoNT is the etiological agent of human and animal botulism. As extensively reported elsewhere, the BoNT mechanism of action consists of the following steps: binding of heavy chain to

polysialoganglioside and probably other protein receptors on the neuronal membrane, internalization of active toxin into endosomal like compartments, membrane translocation facilitated by HN (Heavy chain N- terminal) and enzymatic cleavage of target proteins by the Light chain (Schiavo, and Montecucco, 1997).

In intoxication the toxin will withstand the acid environment of the stomach. As it enters the small intestine, digestive enzymes (e.g. trypsin) or bacterial protease will react on the toxin transforming it into active form. The active toxin is absorbed in the small intestine by binding to the receptors on the apical surface of gut epithelial cells. It is then released into the general circulation (blood stream), and reaching all peripheral cholinergic nerve endings (synapses), which include the neuromuscular junction and autonomic synapses. All botulinum toxin types contain 150-kd polypeptide chains; a100-kd heavy chain joined to a50-kd light chain by a disulphide bond (Dressler, 2012).

The light chain is globular protein with zinc endopeptidase activity in which it cleaves neuronal SNARE (soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor) protein involved in synaptic transmission. The heavy chain has two domains; the N-terminal translocation domain and the C-terminal receptor binding domain. N-terminal consists of α-helices that facilitate the passage of the light chain into the cytosol of the nerve cell. C-terminal is important for the association of the toxin with the target cell. Variation in the receptor binding affinity may describe the differences in susceptibility to *C. botulinum* toxins (Sykes, 2014).

After binding to nerve cell receptors the toxin light chain is internalized through receptor mediated endocytosis. Once inside the nerve terminal the light chain hydrolyzes the SNARE proteins. Different botulinum toxin types hydrolyze different SNARE proteins toxin type A and E hydrolyzes SNAP-25 (synaptosomal associated proteins), type B, D, F, and G hydrolyze VAMP (vesicle associated membrane protein, also known as synaptobrevin) and type C hydrolyzes both SNAP-25 and syntaxin. The SNARE proteins constitute the core of the vesicular fusion machinery enabling fusion of neurotransmitter vesicles with the neuronal plasma membrane and permits release of acetylcholine into the synaptic cleft (Smith, 2009).

This causes depolarization of the muscle membrane and muscle contraction in normal physiological conditions. Cleavage of these proteins under pathological conditions prevents membrane fusion and release of acetylcholine from the nerve cell. In these sites, the toxin binds to specific receptors and is internalized into the cytosol of the nerve terminus, where it blocks the release of acetylcholine, producing the characteristic acute flaccid paralysis and the nerve impulse stops. When this affects respiratory muscle death due to respiratory failure occurs (Simpson, 2004).

2.7. Clinical findings

2.7.1. Clinical signs of animals

All forms of botulism are characterized by progressive, symmetrical, flaccid paralysis that often starts in the hindquarters with weakness, muscle tremors, stumbling, and recumbency and often results in death. The speed of progression is variable, resulting in peracute, acute, and chronic forms of the disease. Some cases may present as sudden deaths. Depending on the amount of ingested toxin, initial signs may be subtle or overt. Generally, the clinical signs appear from 24 hours up to 17 days. In monogastric animals, the incubation period of foodborne botulism is usually shorter than for ruminants, in which clinical signs may be absent for over a week. For toxicoinfectious forms, the incubation period is usually longer, and an indicative period of 4 to 14 days (Deprez, 2006; Hogg.*et al*., 2008).

Signs of the intoxication include reluctance of the animals to rise; the lying posture may be abnormal, and, on rising, the gait may be stilted and the hind limbs splayed and ataxic. Weakness then progresses to the forequarters, head, and neck. Apparent lethargy, depression, and dullness of expression may be the results of loss of tone around the eyes and mouth. The eyes may appear closed, the pupils dilated, and pupillary reflexes sluggish (Critchley, 1991).

Clinical signs in Cattle**:** Cattle in the early stage of the disease appear listless, reluctant to move, and stiff. Weakness in the hind limbs results in difficulty rising, and affected cattle therefore often appear recumbent. Dysphagia is present in most, cases of botulism in cattle. Decreased masseter tone, decreased tongue strength, and pharyngeal paresis or paralysis may contribute to dysphagia, each in variable degree. At this stage the animals remain bright and alert and usually are able to eat the grass around them and drink water from a bucket. As the paralysis progresses, they may become unable to eat and drink, they may be laterally recumbent with terminal abdominal breathing, and the tongue may lose reaction strength and become completely paralyzed. Other clinical signs include photophobia, sluggish rumen movements, reduced anal tone, and tail paralysis (Sharpe et al., 2008). Atypical clinical presentation can appear in cattle because of the ingestion of BoNT type B, are diarrhea, profuse salivation, regurgitation, and vomiting (Hogg *et al.,* 2008).

Clinical signs in Horses**:** Actually the clinical signs in horses are similar to in cattle. The main signs

in adult horses are generalized muscle weakness and dysphagia, decreased tail, eyelid, and tongue tone, mydriasis, and prolonged pupillary light reflex, frequently followed by recumbency, respiratory failure, and death. Additional signs including, anorexia, weight loss, colic, hyper salivation, and tachycardia are common. Inability to eat, drooling or and recumbency are the first signs noticed by the owners. Dysphagia, manifests as milk exiting the nostrils in foals during nursing, accompanied by coughing. In adults, feed material exits the nostrils when the horse attempts to swallow feed, resulting in green, feed tinged discharge coming from the nose. Horses with type C botulism may have more prominent mydriasis, more labored breathing, or less dysphagia than horses with type A or B botulism (Deprez, 2006; Wylie, and Proudman, 2009; Johnson *et al*., 2010 and 2012).

In foals, shaker foal syndrome appears to be similar to infant botulism. The initial presenting sign is often the onset of muscle tremors leading to recumbency. Dysphagia; constipation; reduced eyelid, tongue, and tail tone; mydriasis; sluggish papillary light reflexes; and frequent urination may also be seen (Wylie, and Proudman, 2009).

Clinical signs in birds: In birds, the flaccid paralysis progresses cranially from the legs, to include wings, neck, and eyelids. Initially, affected birds are unable to sustain flight or show uncoordinated flight and may be found sitting and reluctant to move. They seem lame, inability to hold the head erect and the wings may droop when paralyzed. Birds may also appear lateral or ventral recumbent and comatose or dead (Critchley, 1991; Neimanis *et al.,* 2007; Hogg *et al*., 2008).

Recumbent birds intermittently stand and walk a few steps. Often they cannot stand up completely and even walk on their tarsometatarsi. More severely affected water birds are unable to walk and drag themselves forward using their wings and beak (Rocke and Friend, 1999; Neimanis *et al*., 2007). Broilers generally appear ruffled and often show defeathered areas on the back. Affected chickens may have soiled vents caused by diarrhea (Sharpe *et al.,* 2011).

Clinical signs in Fur Farm Animals**:** In fur farm animals, the most typical clinical picture includes the same clinical signs as those in large domestic animals. Paralysis of the hind legs, total paralysis, and recumbency are common. Foxes with milder symptoms often take a sitting position, dragging the rear part of their bodies. In ferrets, clinical signs include weakness, ataxia, ascending paralysis, blepharospasm, photophobia, and urinary incontinence, with death resulting from respiratory failure. The progression of botulism can be very fast in fur animals. Minks are the most susceptible. In some cases, animals that have appeared well have died only 2 or 3 hours later (Lindstro *et al*., 2004).

2.7.2. Clinical signs of humans

The *botulinum* toxin produced by *C. botulinum* is a neurotoxin that causes descending, flaccid paralysis of the muscles, including respiratory system which leads to Respiratory failure. Four distinct naturally occurring forms of human botulism have been recognized and all forms are associated with an acute, a febrile, symmetric, descending flaccid paralysis. The symptoms of botulism are varying with the type of toxin produced rather than the site of its production (Heymann, 2008).

The clinical syndrome of botulism, whether foodborne, infant, wound, or intestinal colonization, is dominated by the neurologic symptoms and signs resulting from a toxin-induced blockade of the voluntary motor and autonomic cholinergic junctions and is quite similar for each cause and toxin type (Arnon, 1992). Incubation periods for foodborne botulism are 6 hours to 10 days, but generally the time between toxin ingestion and onset of symptoms ranges from 18 to 36 hours (St. Louis *et al.,* 1988; Woodruff *et al*., 1992).

Typical clinical symptoms of all forms of botulism are a result of muscle paralysis from affected cranial nerves. These symptoms include double and blurred vision, slurred speech, difficulty swallowing and facial paralysis, dry mouth, diarrhea, nausea, and muscle weakness that descends through the body. Recovery occurs with prompt administration of an antitoxin that blocks the action of the botulinum toxin in the body. In cases of severe botulism, patients may require respiratory intensive care for weeks or months until the paralysis alleviates (Lindstrom and Korkeala, 2006; CDC, 2014).

Infants are not able to complain about the early effects of botulinum intoxication, the neurologic dysfunction associated with infant botulism often seems to develop suddenly. The major manifestations are poor feeding, diminished suckling and crying ability, neck and peripheral weakness (the infants are often admitted as "floppy babies"), and ventilatory failure. Constipation is also often seen in infants with botulism, before the onset of neurologic abnormalities. Loss of facial expression, extraocular muscle paralysis, dilated pupils, and depression of deep tendon reflexes are more frequent with type B than with type A infant botulism (Arnon, 1992; Shapiro *et al*., 1998).

2.8. Diagnosis

Clinical signs of animal are often strongly indicative of botulism, but lacks specificity. A presumptive diagnosis is done based on a combination of clinical signs in sick animals, history, postmortem

findings and by ruling out other differential diagnoses (Rocke and Friend, 1999).

In horses, weakness, decreased eyelid tone, decreased or absent tongue tone, decreased tail and anal tone, sluggish pupillary light reflex, and occasional episodes of slow and uncoordinated padding used for diagnosis. Horses that feed in a group, the dominant horse eats first and is therefore usually the first one to develop clinical signs and shows most rapid progression of the neurotoxic syndrome. In cattle, clinical signs (flaccid paralysis), epidemiology of the outbreak, clinical chemistry and neutrophilia support the diagnosis (Sharpe *et al.,* 2008; Ostrowski *et al.,* 2012)

For the mouse protection test, blood is collected from a sick or freshly dead animal and the serum fraction is inoculated into two groups of laboratory mice, one group of which has been given type-specific antitoxin. The mice receiving antitoxin will survive, and those that receive no antitoxin will become sick with characteristic signs or die, if botulism toxin is present in the serum sample. The ELISA is an *in vitro* test that detects inactive as well as biologically active toxin. During outbreaks it is common to find healthy, sick, and dead animals in the same area (Rocke and Friend, 1999).

Botulism is probably substantially under diagnosed but diagnosis is not difficult when it is strongly suspected, as in the setting of a large outbreak, but since cases of botulism most often occur singularly, the diagnosis may pose a more perplexing problem. They may be diagnosed only retrospectively after death, when the subsequent clustering of cases of botulism-like illness finally alerts public health personnel to an outbreak of botulism after misdiagnosis. Other cases are undoubtedly missed entirely. Entire outbreaks may even go undetected despite severe illness in patients (St. Louis *et al* 1988).

Foodborne botulism: Diagnosis is made by detecting botulism toxin in serum, stool, or implicated food or by culturing *C. botulinum* from stool. Vomitus or gastric aspirate can be tested for toxin if obtained within a few hours of food ingestion. Often the symptoms of foodborne botulism are mistaken for symptoms associated with stroke, chemical intoxication, myasthenia gravis, or Guillain-Barre syndrome. Tests such as brain scans, spinal tap exams, nerve conduction exams, electromyography (EMG), and a tensilon exam can distinguish the above diseases from botulism (Woodruff *et al.,* 1992; CDC, 2014).

Wound botulism: Diagnosis is made by detecting botulism toxin in serum or by culturing *C. botulinum* from an infected wound. Stool should be obtained in addition to rule out foodborne botulism if patient history is unavailable or implicates risk foods. Infant botulism: Diagnosis is made by detecting botulism toxin in stool or by culturing *C. botulinum* from stool. In contrast to foodborne and wound botulism, in cases of infant botulism, the toxin is rarely detected in serum and collection of serum is not recommended (Woodruff *et al.,* 1992).

Based on clinical pathology; There are no changes in hematological values or serum biochemistry that are specific to botulism. Hypophosphatemia may be present and Muscle enzyme activities may also moderately elevate. In foals, arterial blood analysis shows acidemia, hypercapnia, hypoxemia, and desaturation of hemoglobin (Wilkins and palmer. 2003).

Laboratory diagnosis of botulism in the live or dead animal is difficult because of the lack of sensitive confirmatory laboratory tests. Demonstration of BoNTs or spores in serum, feed material, or intestinal content by the mouse bioassay and Detection of antibody in recovering or clinically normal at risk animals are important laboratory confirmation of botulism (Whitelok and Buckley, 1997; Wilkins and palmer, 2003).

Based on necropsy findings; no specific changes detectable at necropsy, although the presence of suspicious feedstuffs in the fore stomachs or stomach may be suggestive. There may be nonspecific subendocardial and subepicardial hemorrhages and congestion of the intestines. Per vascular hemorrhages in the corpus striatum, cerebellum, and cerebrum are nonspecific Microscopic changes in the brain. The presence of toxin in the gut contents is confirmatory if found but is often absent, because the toxin may have already been absorbed. The presence of the toxin in the liver at postmortem examination is taken as evidence that the disease has occurred. In addition to mouse protection test, ELISA techniques, and immuno-polymerase chain reaction (PCR) assay are used for toxin detection (Chao, 2004; Radostits *et al.,* 2006).

2.9. Differential Diagnosis

2.9.1. Differential Diagnosis of animals

In cattle, Differential diagnosis includes parturient paresis (hypocalcaemia), hypomagnesaemia, carbohydrate overload, and toxicosis, including from mycotoxin, lead, nitrate, organophosphate, atropine or atropine-like alkaloid, tick paralysis, tetanus and paralytic rabies (Sharpe *et al*., 2008).

In horses, Differential diagnosis includes toxic plant poisoning, organophosphate intoxication, equine viral encephalitis, central nervous system trauma, equine protozoal myeloencephalitis, aberrant larval migration, tetanus, rabies and hyperammonemia (Ostrowski *et al.,* 2012; Skyes, 2014).

Avian botulism most often affects waterfowl in the season when they are flightless because of wing molt. It is therefore essential to distinguish between

birds in molt and birds with early stages of botulism, since the behavior of these birds may be similar. Molting birds are very difficult to catch, whereas birds that are suffering from botulism can easily be captured when they lose the ability to dive to escape pursuit. Birds at this level of intoxication still have a high probability of surviving if they are properly treated (Rocke and Friend, 1999).

2.9.2. Differential diagnosis of humans

The differential diagnosis in human includes myasthenia gravis, stroke, Guillain-Barré syndrome, bacterial and chemical food poisoning, tick paralysis, chemical intoxication (e.g., from carbon monoxide, barium carbonate, methyl chloride, methyl alcohol, organic phosphorus compound, or atropine), mushroom poisoning, medication reactions (e.g., from antibiotics such as neomycin, streptomycin, kanamycin, or gentamicin), poliomyelitis, diphtheria, and psychiatric illness. In infant botulism, sepsis (especially meningitis), electrolyte-mineral imbalance, metabolic encephalopathy, Reye syndrome, Werdnig-Hoffman disease, congenital myopathy, and Leigh disease should also be considered (Huges *et al.,* 1981; Shapiro, 1998).

Routine laboratory studies are not helpful in confirming the clinical suspicion of botulism. Serum electrolytes, renal and liver function tests, complete blood tests, urinalysis, and electrocardiograms will all be normal unless secondary complications occur. A normal cerebrospinal fluid (CSF) examination helps differentiate botulism from Guillain-Barré syndrome, although a slightly elevated CSF protein level is occasionally seen with botulism, and the protein level might be initially normal in Guillain-Barré syndrome (Shapiro, 1998).

2.10. Treatment and prognosis

Botulism is life threatening condition, administration of antitoxin is the only specific therapy and it is effective only if given very early in the course of neurologic dysfunction**.** When botulism is suspected, the first critical therapeutic step is to give polyvalent antitoxin to affected animals. Antitoxin treatment should be initiated as soon as possible, because it is effective only against circulating toxin and not when toxin is fixed at the neuromuscular junction. Antibiotic administration is indicated only when there is a suspicion of inhalation pneumonia or wound infection. Clostridiocidal drugs may lyses vegetative cells of BoNT producing clostridia, thereby increasing the amount of free toxin in the intestinal tract. Aminoglycosides may potentiate neuromuscular weakness and a non-depolarizing type of neuromuscular block. Although antibiotic treatment is discouraged, beta-lactams have been successfully used to treat poultry affected by the toxicoinfection form of botulism. Other therapies include supportive care (oral water and electrolytes) and reduced physical activity (Jean *et al*., 1995).

For cattle, vaccination can be considered to be effective as atherapeutic treatment in an outbreak situation. Waterfowl can recover from botulism by being administered antitoxins or being provided fresh water and shade. Treated birds should be maintained in pens that provide free access to fresh water, shade, the opportunity for recovered birds to fly out, and minimal disturbance (Rocke and Friend, 1999). Once the diagnosis has been made, euthanasia is frequently advised to avoid problems in maintaining the animals' welfare. Prognosis in recumbent animals is poor. Antitoxin treatment improves the prognosis, but the results are variable. Prevention is preferred for animals in risk. (Hogg *et al*., 2008)

The main steps of treatment of foodborne and wound botulism are: administration of *botulinum* antitoxin in an attempt to prevent neurologic progression of a moderate, slowly progressive illness, or to shorten the duration of ventilatory failure in those with a severe, rapidly progressive illness; careful monitoring of respiratory vital capacity and aggressive respiratory care for those with ventilatory insufficiency (monitoring of respiratory vital capacity should be performed as soon as diagnosis of botulism is made); and meticulous and intensive care for the duration of the often prolonged paralytic illness. Foodborne Botulism or Intestinal/Colonization Botulism*;* Intravenous administration of trivalent (ABE) *botulinum* antitoxin as soon as possible is routine treatment (Tackettco *et al*., 1984; Heymann, 2008).

Wound Botulism*;* Penicillin or metronidazole should be given to patients with wound botulism following antitoxin administration. The wound should be debrided even if it appears to be healing well (WHO, 2002; Pegeus and Miller, 2010).

Infant Botulism*;* Human-derived antitoxin (BabyBIG®) is indicated for the treatment of infant botulism caused by type A or type B toxin. Equine-derived antitoxin is generally not recommended for infant botulism, because of the potential risk of anaphylaxis, serum sickness or the sensitization (lifelong hypersensitivity) of the infant to horse antigen. Equine antitoxin neutralizes only toxin molecules yet unbound to nerve endings (WHO, 2002; AAP, 2012).

2.11. Control and prevention

The growth of *C. botulinum* and toxin production depends on appropriate conditions in food including: temperature, oxygen level, water activity, pH, the presence of preservatives, and competing micro flora (Johnson, 2000). Commercial canned foods are heated to a sufficient temperature and for a sufficient time to kill the spores. Unheated commercial foods in cans or

jars can be made safe by acidification or other manipulations that inhibit the growth of the organism (e.g., addition of phosphoric acid to garlic in oil). Persons doing home canning and other food preservation should be advanced about the proper time, pressure, and temperature required to destroying spores, the need for adequately refrigerated storage of incompletely processed foods, and the effectiveness of boiling, with stirring, home-canned vegetables to destroy botulinum toxins. Heating home-canned foods before consumption can reduce the risk of botulism intoxication. *C. botulinum* may cause container lids to bulge and the contents to have "off-odors." Commercial cans or home-canned products with bulging lids should not be opened, and foods with off-odors should not be eaten or "taste tested." Honey should not be fed to infants because it has been identified as a food source (Benenson, 1995).

In animal the counter measures to prevent or minimize feed borne botulism are based on: providing safe and high quality feed to farm animals, properly storing animal feed, inspecting water sources for dying or dead small animals and birds, avoiding spreading poultry litter that contains birds or dead animals on pastures, avoiding using poultry litter as bedding material, and vaccinating animals (Myllykoski *et al*., 2009).

Preventing botulism can be efficiently achieved by vaccination, which generates neutralizing antibodies against BoNTs. In areas where botulism is endemic, vaccine may be used in animal including cattle, horses, sheep, goats, birds and mink. There is no cross protection against between toxin types and if an animal survives disease it is not protected from later exposure to that toxin (CFSPH, 2010).

Foals can be vaccinated as early as 2 weeks of age. Their immunization can be achieved by vaccinating pregnant mares, considering the high titer of anti-botulism antibodies found in the colostrums. Vaccinated foals or adult horses have to receive an annual booster. Cattle have been routinely vaccinated against type C and type D toxins. Vaccination of cattle with bivalent toxoids conferred considerable immunity following exposure to BoNTs for extended time periods (Steinman et al., 2006; Sprayberry, 2007).

Immunization has been successfully adopted for broilers grown on farms with recurrent cases of the disease and for pheasants and ducks. In waterfowl, immunization might be used to reduce the risk of reintoxication. Usually, 2 doses of vaccine administered about 14 days apart are used. The degree of protection afforded by toxoid vaccination is influenced more by the time and number of inoculations than by the amount of toxoid injected (Dohms, 1982).

In human, only high risk groups such as laboratory workers who work with botulism specimens, or military personnel in risk of botulism when used as biological weapons, are vaccinated (Shapiro et al., 1998).

3. Conclusion And Recommendation

Generally Botulism is a serious neuroparalytic disease of both humans and animals resulting from the action of potent BONTs. It is serious and economically very important due to its mass mortality during outbreaks of the disease. Rapid recognition of the clinical signs and rapid removal of the potential source of botulism toxin or C. botulinum spores is the corner stone to prevent farther spreads of the botulism and enable early administration of specific antitoxin. Without rapid treatment, death is occurring. Strict husbandry and sanitary methods as well as good feeding practices are the crucial way to prevent and control botulism in animal populations. Botulism is always transmitted by ingestion of preformed toxins. It cannot be transmitted directly from diseased animals to humans, but faces, tissues, and body fluids from animals infected with botulism are the potential sources of contamination. Outbreaks of botulism in humans have been associated with contaminated canned commercial foods. Failure in one step during food processing can be disastrous, as the potentially toxic products may rapidly distribute Globally. Botulism can be caused from unsuccessful heating, failure of packing, or storage at temperatures allowing spore germination, and neurotoxin (BONTS) production. Outbreaks of botulism are also typically the result of preparation of traditional fermented foods that are eaten without heating. Educate the population about the risk factors of botulism will contribute to efforts to strengthen the prevention and control methods.

Based on the above conclusion the following recommendations are forwarded .

- Avoid consuming of canned foods in bulging containers, expired and damaged cans.
- If consuming home-canned foods of low acidity, heat to at least 80°C (176°F) for 10 minutes. Canned corn, spinach, and meats should be heated for 20 minutes.
- Properly dispose contaminated material or Burn or bury all carcasses, bones or rotting material and prevent stock access to animal carcasses.
- In dry months give the animals a supplement containing phosphate and calcium.
- Take care during harvesting and storage of feeds and check water sources for organic matter contamination .

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