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Food Poisoning Caused by Bacteria (Food Toxins)

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Abstract

In the environment, there are polluting substances that can cause adverse reactions in human beings when entering the body through different ways (ingestion, inhalation, injection, or absorption). The main pollutants can be poisons, chemical compounds, toxic gases, and bacterial toxins. These can be found in different places and their effects depend on the dose and exposure time. Furthermore, foodborne diseases (FBDs) can cause disability; these diseases can be caused by toxins produced by bacteria or other toxic substances in the food, which can cause severe diarrhea, toxic shock syndrome, debilitating infections such as meningitis and even death. FBDs are transmitted through food contaminated with pathogenic microorganisms that have multiple factors of virulence, which gives them the ability to cause an infection; some bacterial genres can produce toxins directly in the food, but other genres can produce them once they have colonized the intestine. Among the pathogens involved in FBDs that are also considered to be toxigenic are *Salmonella* spp., *Vibrio parahaemolyticus*, *Vibrio cholerae*, *Staphylococcus aureus*, *Clostridium botulinum*, *Clostridium perfringens*, *Bacillus cereus*, *Listeria monocytogenes*. Foodborne diseases can be prevented and acute diarrhea syndromes, fever and even death from dehydration can be avoided, especially in children under the age of 5 and in immunocompromised people.

Keywords: toxins, bacteria, food poisoning, food-borne disease

1. Introduction

The main pollutants can be poisons, chemical compounds, toxic gases, and bacterial toxins. There are several diseases that human beings can acquire by ingesting some type of

pollutants, for example, chemical contamination can lead to acute poisoning or long-term diseases such as cancer. Furthermore, foodborne diseases (FBDs) can cause disability; these diseases can be caused by the toxins produced by the bacteria or other toxic substances in food [1].

It is important to know that poisoning is the cause of morbidity and mortality worldwide. There are different types of intoxication: (a) intoxication caused by chemical substances (such as drugs, pesticides, heavy metals, gases, and solvents) where the patient has direct contact with the toxic substance, and (b) food poisoning, of which the transmission vehicle is contaminated food with pathogens or chemical products. Nowadays, chemical poisoning is a health problem; about six million chemicals are known, of which 80,000 to 100,000 are commonly used in different daily products. In 2006, the World Health Organization (WHO) estimated that more than 25% of poisonings and 5% of cases of cancer, neuropsychiatric disorders, and vascular diseases worldwide were caused by chemical exposure [1, 2].

It is difficult to diagnose chemical poisoning, since a chronological record of the patient's life is required, considering the exposure routes, dose, and time of exposure to the chemical. However, there are protocols that facilitate the diagnosis of chemical poisoning and how to treat incidents from chemical poisoning [1].

Furthermore, food poisoning or foodborne disease (FBD) is one of the main problems in public health worldwide. According to the WHO, each year 600 million people around the world, or 1 out of 10, become ill after consuming contaminated food. Among all these people, 420,000 die, including 125,000 children under 5 years of age, due to the vulnerability of this population to develop a diarrheal syndrome, about 43% of FBDs occur in these patients. About 70% of FBDs result from food contaminated with a microorganism [2–4].

Among the microorganisms causing FBDs are bacteria that have different virulence factors that give them the ability to cause a disease; among these factors, we can find toxins that can be produced in food or once the pathogen has colonized the digestive tract.

It is to be noted that the aim of this chapter is to convey information about some characteristics of the main pathogens producing toxins in food, the diseases they can cause, their complications and treatment options as well as the main sources of contamination in restaurants or street markets.

1.1. Types of bacterial toxins

A bacterial toxin is a macromolecule mainly of protein origin, which can cause toxic damage in a specific organ of the host [5]. Toxins can be divided in endotoxins and exotoxins:

- Endotoxins or lipopolysaccharides (LPS): These are the components of the outer membrane of the Gram-negative bacteria; they are considered the most important antigen of the

bacteria; they are released into the medium after different processes such as lysis and cell division. This endotoxin is capable of causing endotoxic shock and tissue damage [5–7].

LPS are formed by three regions [7]:

- Lipid A is a glycolipid formed by a disaccharide (glucosamine) bound to fatty acids, that are usually capric, lauric, myristic, palmitic, and stearic acids, which are inserted in the outer membrane of the bacterium.
- The nucleus a heteropolysaccharide derived from hexoses and heptoses.
- Lipid A and the nucleus are bound by the sugar acid 2-keto-3-deoxyoctanate (KDO).
- The O chain is a repeating unit polymer of 1–8 glycosidic residues; this polymer is highly variable among bacterial species and genus.

In addition to the pyrogenicity of the endotoxin, an important role has been attributed to the adherence mechanism of the bacteria to the host cell; since in previous studies, it has been observed that when LPS is modified or not expressed, the adherence observed is modified or inhibited.

- Exotoxins: These are the macromolecules of protein origin, which are produced and later released to the medium by the microorganism. Depending on their mechanism of action, exotoxins are divided as follows:
 - Toxins Type I. These toxins modify the host's cells without internalizing in the cells; for example, the superantigens produced by *Staphylococcus aureus* and *Streptococcus pyogenes*.
 - Toxins Type II. Within this group there are hemolysins and phospholipases; this group of toxins is characterized by pore formation and/or destroying the membranes of the host cells. With this virulence factor, the pathogen can invade the host cell; for example, aerolysin and GCAT protein produced by *Aeromonas* spp.
 - Toxins Type III. These toxins are known as A/B due to their binary structure. Fraction B has the function of binding to the receptor of the cell and fraction A is the unit that possesses enzymatic activity, which, depending on the toxin and its mechanism of action, will be the damage to the cell; for example, the Shiga toxin produced by *Escherichia coli* O157:H7, the Cholera toxin (Ctx) produced by *Vibrio cholerae*, and the Anthrax toxin produced by *Bacillus anthracis* [5, 6].

Exotoxins of Gram-negative enteropathogenic bacteria play an important role in the pathogenesis of diarrheal disease, causing hypersecretion of liquids without the destruction and death of intestinal mucosal cells. These toxins are generically referred to as enterotoxins that are different from cytotoxins [8].

There are also two other groups of toxins, those that alter the cytoskeleton and those with neurotoxic activity; however, some toxins may present activity corresponding to more than one of the groups described in **Table 1**.

Toxin type	Definition
Enterotoxin	It produces a net secretion in ligated intestinal segments without histological evidence of intestinal lesion or damage to nonerythrocytic cells in <i>in vitro</i> tests. It stimulates the increase in the short circuit current (Isc) and the potential difference (PD) in the using chamber without evidence of intestinal damage; this result involves the secretion of (active) electrogenic anions. Additionally, a toxin can impair electrically neutral NaCl absorption, which also results in a net secretion of ions.
Cytoskeleton-altering toxin	It alters the cellular form and has been frequently shown to be caused by the F-actin rearrangement. The toxin can cause limited cell damage but is not lethal, and it may or may not be associated with the evidence of net secretion in <i>in vivo</i> or <i>in vitro</i> disease models in intestinal epithelial cells.
Cytotoxin	It causes cell or tissue damage, usually ending with cell death. The toxin may or may not be associated with net secretion in <i>in vivo</i> or <i>in vitro</i> disease models in intestinal epithelial cells.
Neurotoxins	It involves the release of one or more neurotransmitters from the enteric nervous system. It alters the activity of smooth muscle in the intestine.

Source: Adapted from Sears et al. [8].

Table 1. Classification of enteric toxins.

Toxins produced by pathogens involved in foodborne diseases are as follows:

Cholera toxin (Ctx) (*Vibrio cholerae*), Thermolabile toxin (LT) Thermostable toxin (ST) (Enterotoxigenic *E. coli*), Shiga Toxin (*Shigella dysenteriae* and *E. coli* O157:H7) Botulinum toxin (BTX) (*Clostridium botulinum*), CPE Enterotoxin (*Clostridium perfringens*), Alpha-Toxin, Beta-Toxin, Epsilon-Toxin and Iota-Toxin (*C. perfringens*), Toxin A/Toxin B (*Clostridium difficile*), Enterotoxins (A, B, C1, C2, D and E, G, H, I, J), Toxic Shock Syndrome Toxin (TSST-1), Cereulide, and hemolysin BL (HBL), nonhemolytic enterotoxin (NHE) (*S. aureus*), Citotoxin K or CytK (*Bacillus cereus*) [9–15].

1.2. Epidemiology

The high population growth and the food marketing, have generated pathogens causing FBDs to be quickly transported, this has produced outbreaks in different regions, affecting the morbidity, mortality, and economy of the population involved. The trend seen in the United States, the United Kingdom, and Europe indicates that the incidence of FBDs is increasing; this will be a health problem in the following years [4, 16].

There are different types of genus commonly associated with FBDs such as *Campylobacter* spp., enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), *Salmonella* spp., *Shigella* spp., Shiga toxin-producing *E. coli* (STEC) and *V. cholerae* [4, 17].

A total of 66% of foodborne diseases is caused by bacteria. Major diseases include botulism caused by *C. botulinum*, gastroenteritis caused by *E. coli* strains, Salmonellosis and Staphylococcal poisoning. Moreover, *B. cereus* and *V. cholerae* are bacteria frequently reported as causative agents of toxicoinfection by food [18, 19].

In some countries, food poisoning caused by *S. aureus* is the most prevalent; reports indicate that *S. aureus* can be responsible for up to 41% of food poisoning outbreaks. Although it can affect people of any age, the range with the highest incidence goes from 20 to 49 years of age, where up to 48% of the cases can be concentrated. The main food products related to food poisoning caused by *S. aureus* are chicken and eggs, cakes, pastas, sauces, milk, and its derived products [20].

Globally, the highest number of cases is caused by ETEC, 233 million cases, and *Shigella* spp., 188 million cases; however, the highest numbers of deaths are caused by EPEC, 121,455 deaths; ETEC, 73,041 deaths, and *Shigella* spp., 64,993 deaths. In total, 40% of the cases and 43% of the deaths caused by FBDs occurred in children under the age of 5 years old [17].

Food poisoning caused by *B. cereus* can occur any time of the year; it does not present a defined geographical distribution, and because it is naturally found in the environment, its distribution in various types of food occurs easily, especially in those of plant origin such as cereals and rice. Reports about food poisoning outbreaks caused by *B. cereus* are underestimated due to the lack of diagnostic tools; however, globally, there are figures where food poisoning caused by this pathogen occupies from 1 to 17.5% of the total cases of food poisoning caused by bacteria [21, 22].

Food poisoning caused by *C. botulinum* is less frequent and the epidemiological information about it is scarce; outbreaks of food poisoning caused by this pathogen usually include members of one family, that is, they do not involve a large number of individuals and the main cause of such outbreaks is the consumption of canned food at home [23, 24].

Food poisoning caused by *C. perfringens* occurs at any time of the year, but it is more frequent in the last months of the year. It does not present a geographical distribution; in some countries like the United States, the outbreaks caused by this pathogen occupy the second place in foodborne diseases. Generally, this type of outbreaks affect a large number of individuals, therefore, they have a high range of morbidity. In total, 90% of the cases are caused by the intake of meat and poultry products; the contamination of meat and other food products occurs by the contact of pipelines with feces or contaminated surfaces [24, 25].

Nevertheless, the distribution of pathogens varies depending on the region, due to cultural and economic factors that allow both incidence and mortality to be different for each pathogen associated with FBDs. For example, in Europe, *Campylobacter* and *Salmonella* are reported pathogens; their reservoirs are livestock and domestic animals, and food contamination is produced due to bad practices in the food production chain and by cross-contaminations; however, although they play an important role in enteric diseases, they are less frequent than in countries defined by the World Health Organization (WHO) as high-mortality countries (Western Pacific Region and Africa Region), where the sanitary conditions and food and water contamination are factors that increase the incidence and mortality of these genera [17].

In 2010, WHO wrote a report about the main pathogens involved in FBDs, dividing all countries in regions; these regions were grouped based on adult and infant mortality (**Figure 1**).



Figure 1. Geographical distribution of countries by region. Subregions are defined on the basis of infant and adult mortality. Stratum/Layer A = very low infant and adult mortality; stratum B = low infant mortality and very low adult mortality; stratum C = low infant mortality and high adult mortality; stratum D = high infant and adult mortality; and stratum E = high infant mortality and very high adult mortality. AFR: African subregion, AMR: American subregion, EMR: Eastern Mediterranean, EUR: European subregion, SEAR: South-East Asian subregions, WPR: Western Pacific subregion. Adapted from World Health Organization [26].

The risk group causing FBDs depends on the region, in developing countries such as African regions, South America, and South Asia, pathogens causing diarrheal diseases and the invasive pathogens causing infectious diseases and bacteria are the group that causes FBDs, followed by some cestodes and helminths; nevertheless, African regions, cestodes, and helminths are the group that causes FBDs because health and economic conditions limit proper food handling and preservation [17, 26].

With the above, as each risk group is different for each region, in the same way, the distribution of the main pathogens involved in FBDs depends on each region, as well as their incidence; however, developing countries continue to show a great number of cases of FBDs. In addition, the prevalence of pathogens in these countries is higher than in developed countries (**Figure 2**) [4, 26].

Additionally, each region has different socioeconomic characteristics, this creates an impact on the incidence and the mortality of FBDs associated with different bacterial pathogens; the *Shigella* genus occupies the first place in deaths in all regions; however, each region shows a different distribution among the genus that produce the highest number of deaths; this is due to the fact that medical care is different in each region, which means that in some regions a genus causes high mortality and in other regions it is only of medical relevance (**Figure 3**) [4, 17, 26].

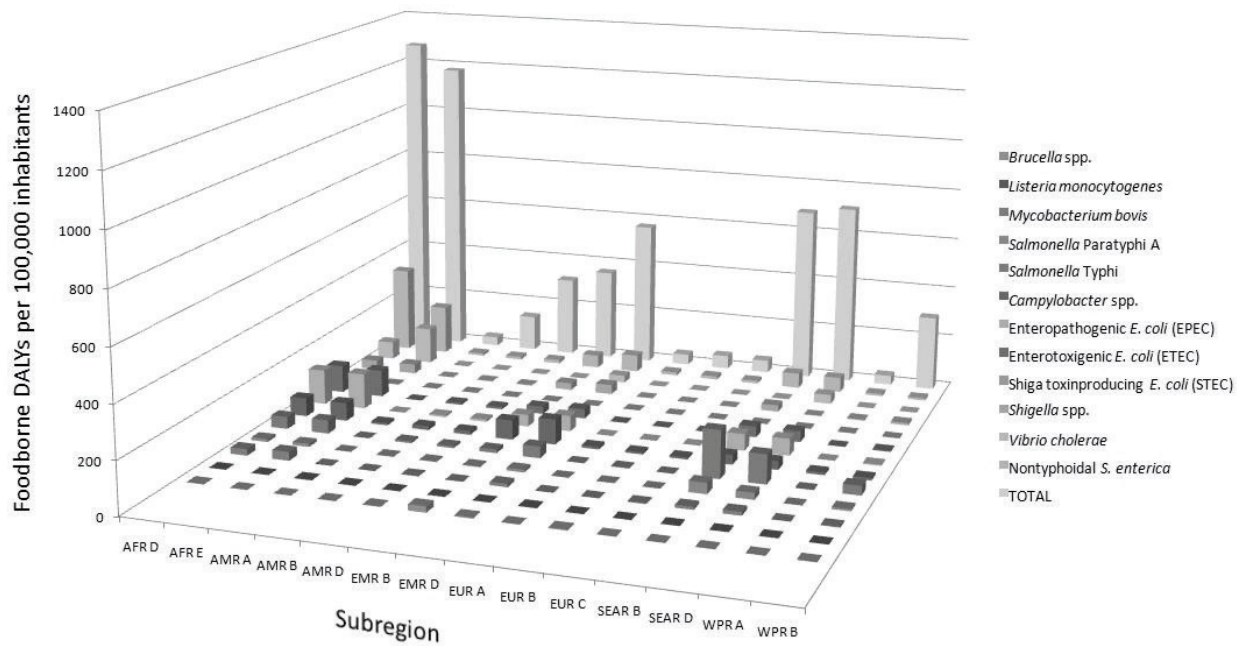


Figure 2. Global burden of FBDs by subregion (DALYs per 100,000 inhabitants) caused by major pathogens. DAYLs: Disability-adjusted life years metric, AFR: African subregion, AMR: American subregion, EMR: Eastern Mediterranean, EUR: European subregion, SEAR: South-East Asian subregions, WPR: Western Pacific subregion. Adapted from World Health Organization [26].

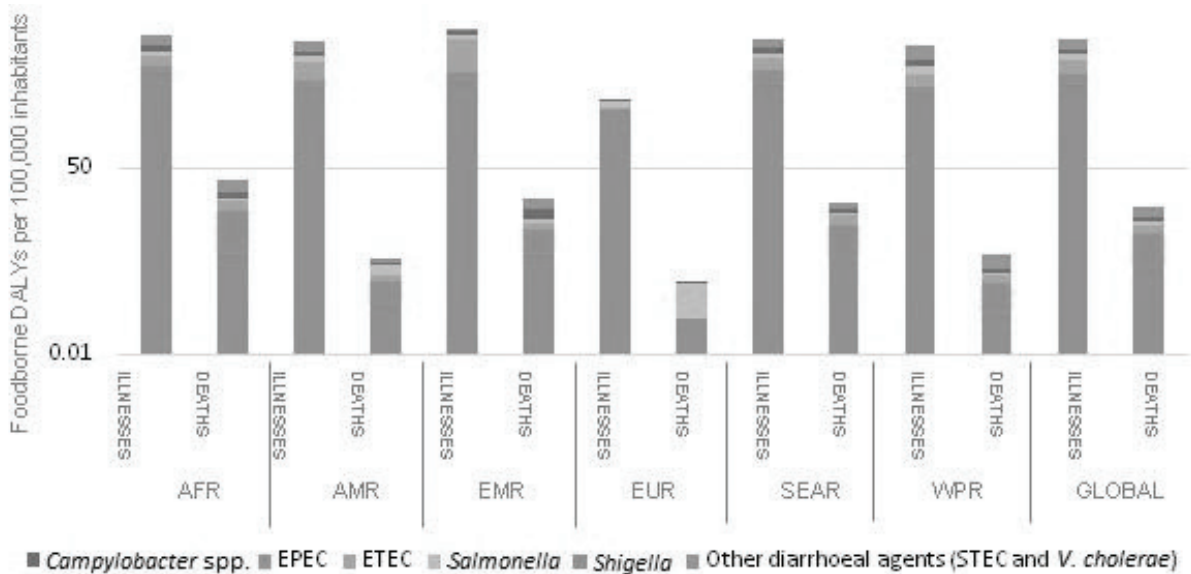


Figure 3. Median rate per 100,000 of diarrheal illnesses and deaths by region. The scale is on logarithmic basis 10. Adapted from Pires et al. [17].

In accordance with the above, it is emphasized the importance of medical authorities to know the incidence of the pathogens causing FBDs that circulate in their regions; not only to know the morbidity and mortality rate, but also to provide the population with the appropriate medical care directed to the pathogen causing FBDs.

2. Risk factors and prevention measures associated with food poisoning

The main risk factor involved in bacterial food poisoning is food contamination by pathogenic bacteria that produce toxins; such contamination can occur at any time, that is, from the crop, in the case of vegetables or, just before eating them, due to the consumer's manipulation; in this way, all the people living on the earth are susceptible to food poisoning. Therefore, food poisoning is a worldwide public health problem, generally the most affected are children, the elderly, pregnant women, and immunocompromised people. As expected, individual factors such as age, gender, place of residence, socioeconomic factors, among others, are crucial in food poisoning acquisition and development [27–29].

Food contamination can occur from primary production to the final consumer, consequently, there are different contamination risks according to the practices carried out in the different stages such as agricultural, livestock, and fish production; industrialization (in the case of processed food); marketing (points of sale), and transportation to the final consumer (homes, community dining rooms, and restaurants) [30].

During the primary production, producers should consider the particular characteristics of the environment where they grow or breed and reproduce livestock, by applying measures to prevent any pollution caused by the air, water, or natural fertilizers. In general, the main risk of contamination in primary production is the unsafe agricultural practices such as the use of manure as natural fertilizer and irrigation with sewage, which violates the fundamental principle of preventing, at all costs and contamination of raw materials from fecal matter [31, 32].

Additionally, another important factor to ensure food safety and good quality is the adequate control of time and temperature when cooking, processing, cooling, and storing food. To achieve a good control of such parameters, it is necessary to consider the physical, chemical, and microbiological characteristics of each type of food, for example, water activity, pH and type, and the initial number of microorganisms presented there. Similarly, other aspects need to be taken into account such as shelf life and usage, that is, whether it is a raw, processed, packaged, or ready-to-eat food [33, 34].

Microbiological contamination can occur through direct contact or through air, utensils, contact surfaces, or the handler's hands; therefore, ready-to-eat foods must be separated in space and time from raw or unprocessed foods. In addition, the latter must always be washed or disinfected. In all stages of the food chain, it is indispensable to use water; hence, this could be the main source of food contamination. It is then necessary to control and monitor the type and the source of the water used at each stage; however, when it is used for food handling, water has to be drinkable water that meets the physical, chemical, and microbiological criteria that its name requires [29, 31, 35].

In terms of facilities, it is important to establish and monitor systems that ensure their maintenance, cleaning, and sanitation. These systems also include an adequate waste management and an effective pest control. The latter constitute a potential risk of any type of contamination; that is why it is necessary to implement measures that prevent the entrance of any type

of pests, as well as measures to avoid their nesting and proliferation. Finally, pest eradication must be carried out by any physical, chemical, or biological method that does not represent a threat to health and food safety [27, 31].

Within the food chain, food transportation plays an important role in preventing contamination and proliferation of microorganisms in food; thus, it is necessary to consider measures to prevent any type of contamination and to provide an environment to control the proliferation of pathogenic microorganisms and the production of bacterial toxins. Some important factors to consider during food transportation are temperature, direct exposure to sunlight, humidity, and airflows. At this stage, the type of containers and the type of packaging also play an important role; the aforementioned and transport conditions should be chosen based on the characteristics of the food that is being transported [36].

Another important measure is the information that producers and suppliers offer to consumers regarding the characteristics and proper handling of prepackaged foods; this is why, generally, food must be packaged and labeled in such a way that the consumer has enough information to handle, store, and prepare the products appropriately without threatening his or her health. Labels should also include a batch number allowing rapid identification and market recalls of products potentially being dangerous for human consumption [37, 38].

In general, microorganisms, more specifically bacteria, can proliferate under very different conditions; that is why they can be found in any type of environment. Even though bacteria are good at adapting to the environments they are in, there are certain conditions that promote bacterial growth more than others. These conditions include food, humidity, acidity, temperature, time, and oxygen; all of these are grouped in what is known as FATTOM (Food, Acidity, Time, Temperature, Oxygen, and Moisture). Knowing and avoiding these optimal conditions can help to prevent bacterial growth, bacterial infections, and food poisoning [39–41].

Most foods contain nutrients required for microbial growth, which makes them easy targets for the microorganisms to develop; therefore, perishable. To reduce the breakdown of food and to prevent foodborne diseases, the proliferation of microorganisms under certain conditions must be controlled, as well as the conditions that must be used to reduce food spoilage to lengthen the time during which physicochemical and organoleptic characteristics must be kept under minimum acceptance parameters. Factors affecting the proliferation rate of microorganisms can be considered as intrinsic and extrinsic [42, 43].

2.1. Intrinsic parameters

Intrinsic factors affecting the proliferation rate are more related to the internal characteristics of food products, and the way in which these characteristics maintain or affect the growth of microorganisms; these factors include water activity, pH, oxidation-reduction potential, content and type of nutrients, inhibiting substances, and biological structures [44, 45].

2.1.1. Water activity

It is defined as the amount of water available for the growth of microorganisms; microbial proliferation decreases when water availability also decreases. The water available for metabolic

activity determines the degree of microbial growth instead of the total moisture content. The unit of measurement for the water that microorganisms require is usually expressed as water activity (A_w), which is defined as the water vapor pressure of food substrate, divided by the water vapor pressure of pure water, at the same temperature. This concept is related to relative humidity (RH), thus: $RH = 100 \times A_w$. The approximate optimal A_w for the growth of most microorganisms is 0.99; most bacteria require an A_w greater than 0.91 to grow. Gram-negative bacteria require higher values than Gram-positive bacteria. Most of the natural food products have an A_w of 0.99 or more. Generally, bacteria have the highest requirements of water activity, fungi have the lowest, and yeasts have intermediate requirements. Most bacteria that decompose food do not grow with an A_w less than 0.91, but fungi and yeasts can grow with values of 0.80 or less, including surfaces partially dehydrated. The lowest value reported for bacteria in food is 0.75 for halophytes, while xerophilic fungi and osmophilic yeasts have shown growth at A_w values of 0.65 and 0.61, respectively [46, 47].

2.1.2. pH

The pH is defined as the negative logarithm of hydronium ions concentration; it is considered as a unit of measure to establish acidity or alkalinity levels of a substance, in this case food, and it is determined by the number of free hydrogen ions (H^+). The effects of adverse pH affect at least two aspects of the microbial cell-functioning of its enzymes and nutrients transportation to the cell.

The cytoplasmic membrane of microorganisms is relatively impermeable to H^+ and OH^- ions; its concentration in the cytoplasm remains reasonably constant, despite the wide variations that may occur in the pH of the surrounding medium. When microorganisms are in an environment below or above the neutral level, their ability to proliferate depends on their ability to change the environmental pH to a more appropriate range, since key components like DNA or ATP require a neutral medium [42, 43, 47].

The pH for the optimal growth of most microorganisms is close to neutrality (pH = 6.6–7.5). Yeasts can grow in an acid environment and thrive in an intermediate range (4.0–4.5), although they survive in values between 1.5 and 8.5. Fungi tolerate a wide range (0.5–11.0), but their growth is generally higher in an acid pH (too acid for bacteria and yeast). Bacterial growth is usually favored by pH values closer to the neutral level. Nevertheless, acidophilic bacteria grow on substrates with a pH of up to 5.2 and below that point the growth reduces dramatically [42, 48].

In general, fruits, vinegars, and wines have pH values lower than those required for bacterial growth, so they can usually be decomposed by fungi and yeasts. Most vegetables have pH values lower than those from fruits, and consequently, vegetables are more exposed to bacterial or fungi decomposition. In contrast, most meats and sea products have pH values equal or greater than 5.6, making them susceptible to decomposition by bacteria, fungi, and yeasts [44, 48, 49].

2.1.3. Oxidation-reduction potential

The oxidation-reduction potential (O/R) is an indicator of the oxidizing and reducing power of a substrate; that is, the O/R potential of a substrate can be generally defined as the ease with

which a substrate loses or gains electrons (when a food product loses electrons, it oxidizes, whereas, when it gains electrons it is reduced; thus, a food product that easily gives electrons is a good reducing agent and the one that receives electrons is a good oxidizing agent). To achieve optimum growth, some microorganisms require reducing conditions and others require oxidizing conditions. The O/R potential of a system is expressed with the Eh symbol (when electrons are transferred from one compound to another, a potential difference is created between the two compounds; this difference can be measured and expressed as millivolts [mV]). The more oxidized a substance is, the more positive the electrical potential will be; and the more reduced a substance is, the more negative the electrical potential will be. When the concentration of oxidant and reducer is equal, there is an electrical potential of zero [39].

Saprophytes that are capable of transferring hydrogen as H^+ and e^- (electrons) to molecular oxygen are aerobic; that is, aerobic microorganisms require positive Eh values (oxidized) for their growth, whereas anaerobic microorganisms require negative values of Eh (reduced). Facultative microorganisms can grow under any of the conditions. It has to be considered that maximum and minimum Eh values (in mV) necessary for aerobic and anaerobic growth could be lethal to the other group. Among food substances that help to maintain reducing conditions are the $-SH$ groups in meats and the ascorbic acid, as well as, reducing sugars in fruits and vegetables. Some aerobic bacteria grow better under slightly reducing conditions being known as microaerophiles such as *Lactobacillus* and *Campylobacter*. Most of fungi and yeasts found in food are aerobic, although a few tend to be facultative anaerobes. Regarding the Eh value of food, vegetables, especially juices, tend to have Eh values of +300 to +400 mV; so, it is not surprising to find that aerobic bacteria and fungi are the common cause of decomposition in this type of products. Meats have Eh values around -200 mV; in ground meats, Eh is usually around +200 mV. Various types of cheese show Eh values between -20 and -200 mV [46].

2.1.4. Content of nutrients

Microorganisms have nutritional requirements, most of them need external sources of nitrogen, energy, minerals, as well as vitamins, and related growth factors; these requirements are found in our food, so if they have the right conditions to develop, they will. In general, fungi have the lowest nutrient requirement, followed by Gram-negative bacteria, then yeasts and finally, Gram-positive bacteria, which have the highest requirements [46, 50].

The primary sources of nitrogen used by heterotrophic microorganisms are amino acids. A great number of other nitrogen compounds may serve for this function for several types of organisms. For example, some of them can use free nucleotides and amino acids, while others can be capable of using peptides and proteins. In general, simple compounds like amino acids will be used by almost all of the organisms before attacking more complex compounds such as high molecular weight proteins. The same applies to polysaccharides and lipids [39, 51].

Microorganisms in food tend to use as energy sources, sugars, alcohols, and amino acids. Fungi are the most efficient in the use of proteins, complex carbohydrates, and lipids because they contain enzymes capable of hydrolyzing these molecules into simpler components; many bacteria have a similar capacity, but most yeasts require simpler molecules. All microorganisms need minerals, although vitamin requirements vary. Fungi and some bacteria can

synthesize enough B vitamins to meet their needs, while others need to have a source of vitamins, food products being an excellent source of them [39, 50].

Gram-positive bacteria are the ones that have lower synthesized capacity, so they need one or more of these components to grow. In contrast, Gram-negative bacteria and fungi are capable of synthesizing the most, if not all, of their requirements and consequently, these two groups of organisms can grow in food products with low content of B vitamins [46, 52, 53].

2.2. Extrinsic parameters

Food factors are very important for the development of microorganisms; there are external or extrinsic factors. This term refers to environmental factors that affect the growth rate of microorganisms; these factors include temperature, oxygen availability, and relative humidity, as well as, the presence and activities of other microorganisms [46].

2.2.1. Storage temperature

Microorganisms have an optimal range, as well as a minimum and maximum temperature to grow. Therefore, ambient temperature determines not only the proliferation rate, but also the genera of microorganisms that are going to be developed, along with the microbial activity degree that is registered. The change in only a few degrees in temperature will favor the growth of completely different organisms, and it will result in a different type of food decomposition and/or foodborne disease. Due to these characteristics, thermal treatment is employed as a method to control microbial activity [46, 54].

The optimal temperature for the proliferation of most microorganisms ranges from 14 to 40°C, although some genera develop below 0°C, and other genera grow at temperatures above 100°C. Nevertheless, food quality must be taken into account when selecting storage temperature. Although it can be desirable to store all food products at temperatures equal or less to those of refrigeration, this is not the best thing to do to maintain a desirable quality in some food products such as banana, whose quality is best maintained in storage at 13–17°C than at 5–7°C. Similarly, many vegetables are favored at temperatures near 10°C such as potatoes, celery, cabbage, and many others. In each case, the success of storage temperature depends, to a large extent, on the relative humidity and the presence or absence of gases such as carbon dioxide and ozone [46, 55].

2.2.2. Oxygen availability and presence of other gases in the environment

Like temperature, the oxygen availability determines the microorganisms that will be active. Some have an absolute requirement for oxygen, while others grow in total absence of it, and others may grow with or without oxygen. Microorganisms that require free oxygen are called aerobic microorganisms, while those that thrive in the absence of oxygen are called anaerobic; and those that grow both in presence or absence of free oxygen are known as facultative microorganisms [43, 46, 56].

Carbon dioxide is the most important atmospheric gas that is used to control food microorganisms. Along with oxygen, it is used in packaged food with modified atmosphere. Ozone

is another atmospheric gas with antimicrobial properties, and for decades, it has been used as an agent to lengthen shelf life of certain types of food. Although being effective against a variety of microorganisms, it is a highly oxidizing agent; thus, it cannot be used in food products with high lipid content, as it could accelerate rancidity. Normally, ozone levels of 0.15–5.00 ppm in the air inhibit the growth of some bacteria that decompose food as well as yeast growth [46, 57].

2.2.3. *Relative humidity in the environment*

Relative humidity (RH) of the environment is important from the point of view of water activity within food and the growth of microorganisms on surfaces. This extrinsic factor affects microbial growth and can be influenced by temperature. All microorganisms have a high-water requirement, this being needed for their growth and activity [46, 54].

When the A_w of a food product is set at 0.60, it is important that this food is stored under RH conditions that do not allow food to draw humidity from the air and, therefore, it increases its own A_w from the surface and subsurface to an extent where microbial growth can occur. A high relative humidity can cause humidity condensation in food, equipment, walls, and ceilings. Condensation causes wet surfaces, which lead to microbial growth and decomposition. Microbial growth is inhibited by a low relative humidity. When food products with low A_w values are placed in high RH environments, food takes in moisture until they reach balance. Similarly, food products with high A_w lose moisture when placed in an environment with low RH. There is a relationship between RH and temperature that must be taken into account when selecting the appropriate storage environments for food products. Overall, the higher the temperature, the less the RH, and vice versa [46, 54, 58].

Bacteria require higher humidity than yeasts and fungi. The optimal relative humidity for bacteria is 92% or higher, while yeasts prefer 90% or higher, and fungi thrive if the relative humidity is between 85 and 90%. Food products suffering superficial decomposition by fungi, yeasts, and specific bacteria, should be stored under low RH conditions. Poorly packed meats such as whole chickens and beef cuts, tend to suffer a lot of superficial decomposition inside the refrigerator before internal decomposition occurs, usually, due to high RH in refrigerators, and to the fact that the biota decomposing meat is essentially aerobic in nature [46, 59].

Although it is possible to decrease the possibility of superficial decomposition in certain food products by storing them in low RH conditions, it should be remembered that the food itself will lose moisture into the atmosphere under such conditions, and thus, it will become undesirable. When selecting appropriate RH conditions, there should be taken into account both the possibility of superficial microbial growth and the quality that the food product needs to have. By altering the gas atmosphere, it is possible to delay superficial decomposition without lowering the relative humidity [46, 60].

2.2.4. *Presence and activities of other microorganisms*

Some food origin organisms produce substances that can inhibit or be lethal for other organisms; these include antibiotics, bacteriocins, hydrogen peroxide, and organic acids. Bacteriocins produced by lactic acid-producing bacteria originated in various food products

such as meat, are of high interest. Bacteriocins produced by Gram-positive bacteria are biologically active proteins with bactericidal action. Some bacteriocins produced by these bacteria inhibit a variety of food pathogens including, *B. cereus*, *C. perfringens*, *Listeria* spp., *A. hydrophila*, and *S. aureus*, among others [39, 46].

Normally food products can reach the final consumer at home, in community dining rooms, or restaurants. Measures to prevent food poisoning should be implemented at these locations, particularly in areas where large volumes of food are distributed such as cold chain, frozen chain, hot chain, and vacuum cooking. Likewise, in the frozen chain, food temperature is gradually lowered to -18°C and defrosted at temperatures higher than 65°C at the time it will be served to the customer (not before); while in the hot chain, for example, in a buffet, food is kept at temperatures higher than 65°C and it should be consumed within 12 h maximum [61].

Other important measures are the use of food preservation methods, which can be physical or chemical. Within the physical methods, there are the traditional or industrial pasteurization, dehydration, preservation in modified atmosphere, and irradiation. In order to maintain an adequate quality control and to minimize the risk of food poisoning, microbial markers can be used; these markers do not represent a potential health risk, however, a large number of them indicate deficiencies in hygiene and sanitary quality of food products; it also leads to a decrease in the shelf-life and could be related to the presence of pathogenic microorganisms. The main microbial markers are aerobic mesophilic, total coliforms, fecal coliforms, Enterococci, *E. coli*, *S. aureus*, and lactic acid bacteria [62].

Once the risk factors are identified, it is necessary to establish a system that allows to prevent and decrease all of them; to do this, a method with scientific basis and systematic profile has been established, this is known as Hazard Analysis and Critical Control Point (HACCP). A microbiological approach should consider the type of microorganism or metabolite (toxins) that threatens human health; the analytical methods for its detection and quantification; the number of samples to be taken and the size of the analytical unit; and the microbiological limits considered to be adequate at specific points in the food chain [63].

3. Foodborne diseases

In food products, we can find different types of toxins such as, bacterial, fungal (mycotoxins), algae or plant toxins, as well as metals, toxic chemicals (zinc, copper, and pesticides), and physical contaminants that can cause diseases in people who eat them; all of these can cause the well-known “foodborne diseases” [64].

Foodborne diseases can be classified into two groups: poisoning and infection.

- Poisoning is caused by the intake of chemical or biological toxins; or toxins produced by pathogens, the latter can be found in food, even if the bacterium is not there.
- Infection is caused by the intake of food containing viable pathogens. Furthermore, a toxic infection (toxicoinfection), formerly known as a toxin-mediated infection, is caused by eating food with bacteria that grow and produce a toxin inside the body [18, 64–66].

To meet the ideal conditions, microorganisms in food grow and produce toxins. By ingesting contaminated food, toxins are absorbed through the intestinal epithelial lining, and it causes local tissue damage. In some cases, toxins can reach organs such as the kidney or the liver, the central nervous system or the peripheral nervous system, where they can cause some damage [18].

The most common clinical symptoms of foodborne diseases are diarrhea, vomit, abdominal cramps, headaches, nausea, pain, fever, vomit, diarrhea with mucus and blood (dysentery), and rectal tenesmus. Some of the microorganisms causing foodborne diseases, either from poisoning, intoxication or toxicoinfection are described in **Tables 2–4**. These diseases are generally diagnosed based on the patient’s clinical record or their symptoms [18–20].

Toxins produced by pathogens involved in foodborne diseases have different characteristics, some of them are shown in **Table 5** [9, 11–15, 67].

3.1. Foodborne diseases caused by bacterial toxins

This section will be addressed to some diseases caused by consuming food contaminated with bacterial toxins or microorganisms that produce them. Among some of the most important diseases are the ones transmitted by *V. cholerae*, *S. aureus*, *B. cereus*, *C. perfringens*, *C. botulinum* and *Listeria monocytogenes*.

3.1.1. *Vibrio cholerae*

V. cholerae has a free life cycle, it is ubiquitous in aquatic environments; it is able to remain virulent without multiplying in fresh water and sea water for a long time. They are more frequent

Bacteria	Disease/medical complications	Food products involved
<i>Salmonella enterica</i> serovar Typhi and <i>Salmonella enterica</i> serovar Paratyphi	Typhoid and paratyphoid fever.	Undercooked pork, beef and poultry, contaminated eggs, and milk.
<i>Salmonella</i> spp.	Salmonellosis (<i>Salmonella</i> Typhimurium, <i>Salmonella</i> Enteritidis).	Undercooked poultry, cauliflowers, and tomatoes.
<i>Vibrio vulnificus</i>	Septicemia in people with underlying diseases or people who are taking immunosuppressive drugs or steroids.	Seafood, usually oysters.
<i>Mycobacterium bovis</i>	Cervical lymphadenopathy, intestinal lesions, chronic cutaneous tuberculosis.	Contaminated milk.
<i>Mycobacterium avium</i> , subspecies <i>paratuberculosis</i>	Crohn’s disease.	Pasteurized milk.
<i>Listeria monocytogenes</i>	Meningitis, encephalitis, sepsis in pregnant women, intrauterine or cervical infection that can lead to miscarriage or birth of a dead child.	Raw beef, pork, poultry, vegetables and milk, cheese, ice cream, smoked fish, and raw fish.

Modified from Refs: [18–20].

Table 2. Pathogens that cause infection.

Bacteria	Disease/medical complications	Food products involved
<i>Clostridium botulinum</i>	Paralysis of arms, legs, trunk, and respiratory muscles.	Mixture of oil and nonacid garlic, potatoes cooked at high temperatures, and stews.
<i>Bacillus cereus</i>	Fried rice syndrome.	Rice cooked at high temperatures, sauces, soups, and puddings.
<i>Staphylococcus aureus</i>	Toxic shock syndrome.	Meat and meat products cooked at high temperatures, poultry, and salads with mayonnaise.

Source: Modified from Refs: [18–20].

Table 3. Pathogens that cause intoxication.

Bacteria	Disease/medical complications	Food products involved
<i>Escherichia coli</i> O157:H7	Hemorrhagic colitis, Hemolytic uremic syndrome in children.	Hamburgers, nonpasteurized milk, contaminated water, spinach, and lettuce.
<i>Shigella</i> spp.	Hemolytic Uremic Syndrome.	Salads, lettuce, raw vegetables, and milk.
<i>Aeromonas</i> spp.	Meningitis, peritonitis, myocarditis, hemolytic uremic syndrome, necrotizing fasciitis in wounds.	Meat (beef, sheep, pork and chicken), vegetables, eggs, fish, seafood, and prepared food.
<i>Cronobacter sakazakii</i>	Permanent neurological or developmental deficits; death.	Powdered infant formula.
<i>Vibrio parahaemolyticus</i>	Gastroenteritis, septicemia and wound infection. Severe infections in immunocompromised people.	Raw or undercooked seafood, usually oysters.
<i>Clostridium perfringens</i>	Clostridial necrotizing enteritis.	Meat juice, stews, cooked beans, meat cooked at high temperatures.
<i>Campylobacter</i> spp.	Campylobacteriosis, arthritis, meningitis, <i>Campylobacter jejuni</i> can cause Guillain-Barré Syndrome.	Cheese made with raw milk and chicken meat.
<i>Yersinia enterocolitica</i>	Yersiniosis, enterocolitis, pseudoappendicitis, mesenteric lymphadenitis, infections in wounds, joints and the urinary tract, and Reiter's syndrome.	Nonpasteurized milk, tofu, nonchlorinated water, undercooked meat, oysters and fish.
<i>Vibrio cholerae</i> serogroup O1 or serogroup O139	Cholera.	Contaminated water and raw seafood.
<i>Vibrio cholerae</i> serogroup no-O1	Less severe than Cholera; gastrointestinal infections, sepsis.	Raw, semicooked or recontaminated fish and shellfish after cooking.

Source: Modified from Refs: [18–20].

Table 4. Pathogens that cause toxico-infection.

Name	Biological effect
Cholera toxin (Ctx) (A-5B)	It activates the adenylyl cyclase; increases the levels of intracellular cAMP promoting fluid and electrolytes secretion in the intestinal epithelium, causing diarrhea. It is a potent exotoxin.
Thermolabile toxin (LT) (A-5B)	Similar effect as the Cholera toxin.
Thermostable toxin (ST)	The binding of ST to the guanylyl cyclase receptor results in an increase of cyclic GMP, affecting the flow of electrolytes. It promotes water and electrolytes secretion from the intestinal epithelium by causing diarrhea.
Shiga toxin (A-5B)	Inactivates the ribosomal subunit 60S and inhibits protein synthesis causing the death of susceptible cells.
Botulinum toxin (A/B)	It is a neurotoxin consisting of a heavy and a light chain linked by a disulfide bond. It is a Zn ⁺⁺ -dependent protease. It inhibits the presynaptic release of acetylcholine from peripheral cholinergic neurons, resulting in flaccid paralysis. The neurotoxin exists in seven different serotypes (A-G).
CPE enterotoxin	Lethal, cytotoxic and enterotoxic activity. Stimulates the adenylyl cyclase allowing the increase of cAMP in epithelial cells, which causes diarrhea.
Alpha-toxin	It produces gas gangrene. It has phospholipase (PLC), sphingomyelinase, hemolytic, and dermonecrotic activities. The mature protein is organized into two domains; the amino-terminal, which contains the PLC activity, and the carboxyl-terminal binding that depends on calcium. Depending on the lipid composition of the cell membrane, the Alpha-toxin may be hemolytic in the presence of calcium.
Beta-toxin	It forms selective pores for monovalent cations in lipid bilayers and sensitive cells membranes, so it functions as a neurotoxin capable of producing arterial constriction.
Epsilon-toxin	Produced and secreted by a prototoxin that, when it suffers a specific proteolytic cleavage, it acquires its maximum biological activity. Activation can be catalyzed by proteases such as trypsin, chymotrypsin, and a zinc-dependent metalloproteinase.
Iota-toxin	It has dermonecrotic, cytotoxic, enterotoxic activities, and it causes intestinal histopathological damage. This toxin is binary and consists of a binding peptide (Ib) and an enzymatic peptide (ADP-ribosyltransferase) (Ia). The first one is necessary to internalize the second one. The Iota-toxin requires proteolytic removal of a propeptide fragment, which allows the Ib unit to be inserted into the membrane and to interact with the Ia portion to form a heptameric pore that allows the K ⁺ and Na ⁺ ions to escape; in addition to the Ia portion entrance into the cell where it ribosylates the G-actin to depolymerize the actin filaments, with the consequent destruction of the cytoskeleton. The Iota-toxin is generally activated by the effect of the proteases present in the intestinal tract.
Toxin A/Toxin B	It modifies the Rho, a subfamily of GTP-binding proteins that regulate cytoskeletal actin. The deamination of the glutamine residue at position 63 of Rho to a glutamic acid produces a dominant-active Rho protein incapable of hydrolyzing the GTP, resulting in cellular necrosis and bloody diarrhea associated with colitis.
Enterotoxins (A, B, C1, C2, D and E, G, H, I, J)	Enterotoxins are thermostable; they differ in toxicity. Staphylococcal enterotoxins are superantigens that cause massive activation of the immune system, including lymphocytes and macrophages; the exact role in emesis is not known.

Name	Biological effect
Toxic Shock Syndrome Toxin (TSST-1)	Superantigen that acts on the vascular system causing inflammation, fever, and shock.
Cereulide	Thermostable peptide, toxic for the mitochondria when acting as a potassium ionophore.
HBL, NHE, Citotoxin K or CytK	HBL is a three-component hemolysin; two protein subunits, L2 and L1 (cytolytic components), and a B protein (favors binding to the host cell), apart from the hemolytic effect, it is cytotoxic, dermonecrotic and causes vascular permeability. NHE also consists of three components (NheA is a cytolytic component and NheB and NheC favor binding to cells of small intestine). Both toxins are organized into operons (<i>hbl</i> and <i>nhe</i>), where the genes encoded the NHE components are transcribed together. CytK forms pores in the epithelial cells membrane, and it has necrotizing and cytotoxic activity.

Note: A-5B indicates that the subunits are separately synthesized but associated by noncovalent bonds during secretion and binding to target. 5B indicates that the binding domain of the protein is composed by five identical subunits. A/B denotes a toxin synthesized as a simple polypeptide divided into domains A and B that can be separated by proteolytic cleavage. HBL: hemolysin BL, NHE: nonhemolytic enterotoxin.

Source: Modified from Refs: [9, 11–15, 67].

Table 5. Main toxins produced by pathogens involved in foodborne diseases and their biological effect.

in temperate waters and can be isolated in seafood and fish. The most notable species are *V. cholerae* O1 and O139, causative serogroups of Cholera. Non-O1 strains and the rest of the species cause cholera-like diarrheal syndromes, but they are not as severe, although they frequently produce extraintestinal infections [68–70].

The CTX toxin (Cholera toxin) is the main virulence factor of *V. cholerae* O1 (Ogawa, Inaba, and Hikojima serotypes, Classical and El Tor biotypes) and O139; it contributes to cause profuse diarrhea, after an incubation period from 2 h to 5 days; stools have the appearance of rice water, there is dehydration and electrolyte imbalance, which can lead to death. Approximately 75% of the infected people are asymptomatic, that is, they do not develop the symptoms aforementioned; however, the pathogen is shed in their feces for 7–14 days, which is a very serious source of contamination since it is possible to infect others. The most vulnerable groups are children, adults, and people infected with the HIV virus [68, 69, 71].

This toxin can be identified by the presence of the *ctxAB* gene. *V. cholerae* no-O1 has the *ctx* gene but it is rarely expressed; nevertheless, a faster test is not yet available, although the WHO is currently in the process of validating new rapid diagnoses. The bacteria can be isolated and identified from stool samples by using laboratory procedures [24, 69, 71].

Efficient treatment resides in prompt rehydration through oral solutions or intravenous fluids. The use of antibiotics is suggested only when there is severe dehydration. The supply of safe drinking water, the adequate sanitation, and food security are essential to prevent the emergence of Cholera. Moreover, vaccines administration has emerged because control measures to prevent contamination are insufficient; this is the reason why oral vaccines have been developed as tools to prevent outbreaks. These vaccines are given to more vulnerable

populations in areas where the disease is endemic. Experience in different mass vaccination campaigns in countries such as Mozambique, Indonesia, Sudan, and Zanzibar clearly indicates that vaccination requires careful and early planning and preparation, and therefore, it cannot be improvised at the last minute [71].

The lack of toxicity combined with stability and the relative ease to express the Cholera Toxin Subunit B (CTB) has contributed to be an easily manageable adjuvant. The ability to express protein in a wide variety of organisms broadens even further its application potential. CTB is currently being used in vaccines such as Dukoral, a vaccine against *V. cholerae* that consists of dead bacteria and recombinant CTB. It has been approved as adjuvant for vaccines in Europe and in Canada; and given the excellent adjuvant effect, this protein is likely to play an important role in vaccine formulation in the future [72].

3.1.2. *Staphylococcus aureus*

Staphylococcal foodborne illness is one of the most common diseases acquired by *S. aureus*. It is one of the most concerned diseases by public health programs in the world; it is due to the production of one or more toxins by the bacteria during their growth at permissive temperatures; however, the incubation period of the disease depends on the amount of ingested toxin. Small doses of enterotoxins can cause the disease; for example, a concentration of 0.5 ng/mL in contaminated chocolate milk has been reported to cause large outbreaks [73].

S. aureus produces various toxins. Staphylococcal enterotoxins are a family of nine thermostable enterotoxin serotypes belonging to a large family of pyrogenic toxins (superantigens). Pyrogenic toxins can cause immunosuppression and nonspecific T cell proliferation. Enterotoxins are highly stable and they resist high temperatures (which makes them suitable for industrial use) and environmental conditions of drying and freezing. They are also resistant to proteolytic enzymes (pepsin and trypsin) at low pH, enabling them to be fully functional in the digestive tract after infection [73].

The mechanism by which poisoning is caused is not entirely clear yet. However, enterotoxins have been observed to directly affect the intestinal epithelium and the vagus nerve causing stimulation of the emetic center. It is estimated that 0.1 µg of enterotoxin can cause staphylococcal poisoning in humans. Apart from causing poisoning, *S. aureus* can also cause toxic shock syndrome due to the production of the Toxic Shock Syndrome Toxin 1 (TSST-1) and Enterotoxin Type B [65, 73, 74].

Symptoms include nausea, vomit, abdominal cramps, salivation, diarrhea could be present or absent. The first three symptoms are the most common ones. Usually, it is a self-limiting disease and can be cured in 24–48 h, but it can become severe, especially in children, the elderly, and immunocompromised people. Toxic shock syndrome is characterized by high fever, hypotension, erythematous rash (similar to scarlet fever, peeling of the skin during recovery, flu-like symptoms, vomiting, and diarrhea) [73–75].

The diagnosis of the disease is carried out by detecting the staphylococcal enterotoxin in the food or by recovering at least 10^5 *S. aureus*/g from food leftovers. The enterotoxin can be

detected by several methods: bioassays, molecular biology, and immunological techniques. The isolated strains can be genetically characterized by multilocus sequences from the *spa* or *SCCmec* gene, and pulsed-field electrophoresis [73].

The mainly involved food products in outbreaks and where *S. aureus* can grow optimally, since they are stored at room temperature, are meat and its derived products, poultry and eggs, milk and its derived products, salads, and bakery products (cream-filled cakes and stuffed sandwiches) [65, 73].

Other factors that must be taken into account are the emergence of methicillin resistant strains, which may be found in food (mainly in meat and milk). It is important to note that many of the isolates obtained from outbreaks are not tested for antimicrobial susceptibility; due to the various problems that these strains can create, the antimicrobial susceptibility test should be performed. They have been reported to be causative agents of outbreaks in blood infections and wounds in immunocompromised patients in hospitals [65, 73].

Foodborne illness due to *S. aureus* may be preventable. It is known that the permissible temperature for the growth and production of the enzyme is between 6 and 46°C; thus, food products could be cooked above 60°C and refrigerated below 5°C. Therefore, maintaining the cold chain of food can prevent the growth of the microorganism. By using good manufacturing practices and good hygiene practices, the contamination by *S. aureus* can be prevented [73].

3.1.3. *Bacillus cereus*

B. cereus is a ubiquitous microorganism in the environment, and it can easily contaminate any food production and processing system, due to the formation of endospores. The bacterium can survive pasteurization and cooking processes [11, 15].

It has been demonstrated that this microorganism produces, cereulide or emetic toxin; three enterotoxins, hemolysin BL (HBL), nonhemolytic (NHE), cytotoxin K (CytK), which are responsible for the emetic syndrome and diarrhea; and three phospholipases, phosphatidylinositol hydrolase, phosphatidylcholine hydrolase, and hemolytic sphingomyelinase. Cereulide is a thermostable cyclic peptide that causes emesis by stimulating the afferent vagal pathway through its bond to the serotonin receptor. The toxin is produced during the stationary phase of growth of the microorganism and it accumulates in food over time. The structure of the toxin explains its resistance to food processing methods. In contrast, inside the small intestine of the host, the thermolabile enterotoxins, HBL and NHE, produced during the exponential phase of the vegetative growth of the bacterium are the cause of diarrheal syndrome; the proteins that form enterotoxins (binding and lithic factors) are unable to traverse intact the gastric barrier; that is why it is considered that preformed or extracellular enterotoxins in food are not involved in the pathogenesis of the bacterium. It is believed that the spore germination that reaches the small intestine, the growth, and the simultaneous production of the enterotoxin are the ones that cause diarrhea. HBL is a hemolysin formed by three components, two protein subunits (L2 and L1), and one B protein; it has hemolytic,

cytotoxic, and dermonecrotic effect, and it induces vascular permeability. NHE also consists of three components: NheA, NheB, and NheC. It has been demonstrated that strains producing emetic toxin do not produce enterotoxin. The cytotoxin K is similar to the Alpha-toxin of *S. aureus* and the Beta-toxin of *C. perfringens* [13, 15, 76].

Furthermore, the enterotoxin FM (EntFM) has been described; it is a 45 kDa polypeptide encoded by the *entFM* gene, located in the bacterial chromosome. It has not been directly involved in food poisoning; however, the presence of the gene in strains that cause diarrheal outbreaks has been detected; in experiments with mice and rabbits, it causes vascular permeability [11].

The emetic syndrome is characterized by nausea and vomit similar to those produced by *S. aureus* poisoning. Symptoms appear soon after consuming food contaminated with the preformed toxin. Generally, poisoning develops with mild symptoms, usually lasting no more than 1 day, but severe cases require hospitalization. The diarrhea that is caused belongs to the secretory type, similar to the one produced by *V. cholerae*. Colic pain occurs similar to that of *C. perfringens* poisoning. Both syndromes are self-limiting [13, 15, 77].

Enterotoxins can be detected by immunoassays or molecular biology (conventional PCR and multiple PCR) by looking for the *ces* gene (nonribosomal production of cereulide); by detecting the *hblD*, *hblC*, and *hblA* genes encoding the L1, L2, and B protein components of the HBL toxin, respectively; or the *nheA*, *nheB*, and *nheC* genes of the NHE toxin components. The 16S ribosomal gene can be looked for by real-time PCR [11, 13, 77].

Apart from causing food poisoning, *B. cereus* can also cause local and systemic infections in immunocompromised patients, neonates, people taking drugs, and patients with surgical or traumatic wounds, or catheters [15].

The most susceptible food products to be contaminated include flours, meats, milk, cheese, vegetables, fish, rice and its derived products; generally, in food with high content of starch. The strains produced by the emetic toxin grow well in rice dishes (fried and cooked) and other starchy products; although, there have been studies where it has been demonstrated that the toxin can be in different types of food products; while strains producing diarrheagenic toxins grow in a wide variety of food products, from vegetables to sauces and stews [15, 77].

Strains isolated from infections have been shown to be sensitive to chloramphenicol, clindamycin, vancomycin, gentamicin, streptomycin, and erythromycin; they are resistant to β -lactam antibiotics, including third-generation cephalosporins [15].

Inadequate cooking temperatures, contaminated equipment, and poor hygiene conditions at the food processing and preparation sites are the major factors that contribute to food poisoning by *B. cereus* and its toxins; that is why, it is suggested to store food at temperatures lower than 4°C or to cook them at temperatures higher than 100°C, and to reheat or cool food rapidly, to avoid prolonged exposure to temperatures that allow spore germination and to diminish the risks of a possible poisoning [11].

3.1.4. *Clostridium perfringens*

C. perfringens is an anaerobic bacterium that creates spores that survive in soil, sediments, and areas subject to both human and animal fecal contamination. It is widely distributed in the environment and is frequently found in the human intestine and in several domestic and wild animals' intestines [78].

C. perfringens is classified into five groups (A, B, C, D, and E), due to the different toxins it produces (alpha, beta, epsilon, and iota). The Alpha-toxin is produced by all the five groups. The Beta-toxin forms selective pores for monovalent ions in the lipid bilayers, functioning as a neurotoxin capable of producing arterial constriction. The Epsilon-toxin is the most potent clostridial toxin after tetanus and botulinum neurotoxins (BoNTs). It is produced and secreted by a prototoxin that acquires its maximum biological activity by undergoing a specific proteolytic cleavage; its activation can be catalyzed by trypsin, chymotrypsin, and a zinc metalloprotease [12].

The toxin receptor is unknown, but it is known to be a surface protein anchored by glycosylphosphatidylinositol. Its main biological activity is the edema generation; it is lethal but not hemolytic. The Iota-toxin is a member of the binary toxin family, since it is formed by a binding peptide (Ib) necessary for the internalization of the enzymatic peptide (Ia; ADP-ribosyltransferase). Proteolytic removal of a propeptide fragment is required to allow Ib to be inserted into the membrane and to interact with Ia. Ib, when inserted into the membrane, forms a heptameric pore that allows the exit of K⁺ and Na⁺ ions, and the entry of Ia, which once inside the cell, is ribosylated by the G-actin; it depolymerizes the filaments of Actin by destroying the cellular cytoskeleton. The Iota-toxin is dermonecrotic, cytotoxic, enterotoxic, and induces intestinal histopathological damage [12].

However, the virulence of this bacterium is not only due to the presence of these 4 toxins; there have also been described 15 toxins within which the CPE enterotoxin is responsible for causing diarrhea in humans and animals, and it is produced by Type A strains. This toxin is associated with 5 or 15% of gastrointestinal diseases in humans different from food poisoning such as diarrhea produced by antibiotics; the NetB toxin is frequently related to necrotic enteritis in birds and the Beta2-toxin is apparently associated with enteritis. The production of toxins in the digestive tract is associated with sporulation. The disease is foodborne; and only one case has implied the possibility of poisoning caused by the preformed toxin [12, 78, 79].

C. perfringens causes food poisoning characterized by severe abdominal cramps and diarrhea beginning after 8–22 h of food intake, the disease ends 24 h after the intake; although, in some cases the disease may persist for 1–2 weeks. Additionally, there is a more severe but less frequent disease caused by eating a food product contaminated with type C strains; this disease is known as necrotic enteritis or pig-bel disease, and it is often fatal. Deaths caused by necrotic enteritis are due to intestinal infection and necrosis, as well as by septicemia, the elderly people being the most affected population [78].

The disease diagnosis is confirmed by the presence of the toxin in the stools of patients; either by traditional methods (culture from the stools or the food involved) or by molecular methods by looking for the following genes: *cpe* (CPE toxin), *plc* (Alpha-toxin), and *etx* (Epsilon-toxin) [12, 78, 79].

Among the main food products involved are meat and its derived products. The disease can be prevented if the food has been properly cooked; although, there may be a risk of cross-contamination if the cooked food comes in contact with raw and contaminated ingredients, as well as contaminated surfaces [78].

There is no specific treatment or established cure for the infections caused by the toxins of the bacteria. Supportive care includes administration of intravenous fluids, oral rehydration salts solutions, and medication for fever and pain control. The treatment of gas gangrene is based on surgical measures with debridement and removal of the affected tissue and administration of high doses of antibiotics. Necrotizing enterocolitis is treated systemically with penicillin G, metronidazole or chloramphenicol; 50% of the cases require surgical treatment in which a segmental jejunum resection is performed. The antibiotics active against anaerobic bacteria are effective; however, there are strains resistant to penicillin and clindamycin, therefore, it is suggested to perform antimicrobial susceptibility tests, especially in patients with severe disease and those requiring long-term treatments [9, 80].

3.1.5. *Clostridium botulinum*

C. botulinum is a spore-forming microorganism; these spores can remain viable for long periods of time when the environmental conditions are absolutely unfavorable for the development of the microorganism [60].

Four groups are recognized in *C. botulinum*, as well as seven antigenic variants of botulinum neurotoxins (A–G). Groups I and II are primarily responsible for botulism in humans; Group III is responsible for causing botulism in several animal species, and Group IV appears not to be associated with the disease in either humans or animals. Group I is also known as *C. botulinum*-proteolytic (mesophilic microorganisms), while group II is known as *C. botulinum*-non-proteolytic (psychrophilic microorganisms). Group I forms spores that are highly resistant to heat, the “Botulinum cook” (121°C/3 min) given to canned foods with a low content of acid is designed to inactivate them; neurotoxins formed in this group are A, B, F, and H. Group II forms moderately heat-resistant spores, and the neurotoxins formed are B, E, and F. Botulism types A, B, E, and F rarely cause the disease in humans, whereas in animals it is caused by types C and D. Toxins are resistant to proteolytic reactions and to denaturation into the gastric apparatus. Botulinum toxins are metalloproteins with endopeptidase activity that require zinc; the general structure shows two chains with a molecular weight of 150 kDa, the double chain is subdivided into a heavy (H) structure constituted by a nitrogen terminal domain (HN), and a carboxyl-terminal (HC), and a lighter structure (L) that performs the catalytic function of the toxin. HC is responsible for binding to presynaptic receptors for internalization, and HN is called translocation domain [81–83].

C. botulinum, is a bacterial species known simply for producing the botulinum toxin. The number of genes in Group II strains coding for the neurotoxin is variable; there may be one to three genes that encode one to three different neurotoxins; if there are two genes, there can be one active toxin and an inactive toxin, or both toxins can be active. In Group II, the presence of only one gene has been described, that is why there is only one neurotoxin; however, in other studies it has been demonstrated that in Type F strains the toxin has part of Type B and

Type E neurotoxins. Botulinum neurotoxins form complexes with accessory proteins (hemagglutinin and nonhemagglutinin), which protect the neurotoxin and facilitate their adsorption into the host. The hemagglutinin complex of the neurotoxin type A specifically binds the cell adhesion protein, E-cadherin, by binding the epithelial cell and facilitating the adsorption of the neurotoxin complex from the intestinal lumen. Dual toxin-producing strains have been isolated from botulism in humans, the environment, and food; recently there have been found strains that produce three botulinum toxins called F4, F5, and A2. The significance of producing two or more toxins on virulence, as well as the evolutionary consequences are not yet clear. Phylogenetic studies show evidence of horizontal gene transfer; the production of the dual toxin in Group I and the production of a single toxin in Group II is still not clear. Therefore, studies with toxins isolated and purified from the different groups of *C. botulinum* are still being carried out [81–83].

Botulism is a severe disease with a high fatality rate. The typical symptoms are flaccid muscle paralysis, sometimes it starts with blurred vision followed by an acute symmetrical decrease of bilateral paralysis that, if untreated, can lead to paralysis of the respiratory and cardiac muscles. If severe cases are not fatal, the patient may improve his/her condition after months or even years. There are three types of botulism: infant/adult intestinal botulism, wound botulism, and foodborne botulism. The first type (infant/adult intestinal botulism) is an infection associated with the multiplication of the microorganism and neurotoxin formation in the intestine; the second type (wound botulism) is an infection associated with cell multiplication and toxin formation in the wound, often acquired after drug abuse; and the third type (foodborne botulism) is a poisoning caused by the consumption of neurotoxin preformed in food. An amount of 30 ng of toxin is enough to cause the disease and sometimes death. Symptoms appear between 2 h and 8 days after the intake of contaminated food, although they may occasionally appear between 12 and 72 h [81, 82].

Botulism can be diagnosed only by clinical symptoms, but its differentiation from other diseases can be difficult. The most effective and direct way of confirming the disease in the laboratory is by demonstrating the presence of the toxin in the serum, in stools of patients, or in food products consumed by them. One of the most sensitive and widely used methods to detect the toxin is through neutralization in a rodent. This test takes 48 h, and culture of specimens takes from 5 to 7 days. Infant botulism is diagnosed by detecting botulinum toxins and the microorganism in the stools of children [78].

Approximately 90% of the reported cases are related to the consumption of home-made preserved food, especially vegetables; the industrial preparation of meat and fish is rarely associated with botulism. Food products where spores of the bacteria or the botulinum toxin can be found are canned corn, pepper, soups, beets, asparagus, ripe olives, spinach, tuna chicken, chicken liver, ham, sausages, stuffed eggplants, lobster, and honey, just to name a few [78, 82].

To prevent the chances of getting botulism through food, it is necessary to carry out appropriate control measures in food processing and handling, especially when new technologies are introduced or modified. Applying the “Botulinum cook” in the modern industry allows to secure canned foods. The use of chlorine and chlorinated compounds can help sanitize places that handle food industrially. Spores can also be inactivated with ozone and ethylene oxide [81, 82].

3.1.6. *Listeria monocytogenes*

L. monocytogenes is a facultative intracellular microorganism widely distributed in nature, capable of surviving both in the soil and the cytosol of a eukaryotic cell. Considering somatic (O) and flagellar (H) antigens, this bacterium can be classified into 13 serotypes (1/2a, 1/2b, 1/2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e, 7), but only the serotypes 1/2a, 1/2b, and 4b are responsible for more than 98% of the cases of human listeriosis. Furthermore, it has also been grouped into four lineages (I, II, III, and IV), where lineage I (serotypes: 1/2b, 3b, and 4b) and lineage II (serotypes: 1/2a, 1/2c, 3a, and 3c) include most strains isolated from clinical cases; lineage I strains have a greater pathogenic potential. Lineages III and IV include strains of serotypes 4a, 4c, and an atypical 4b [84].

L. monocytogenes expresses multiple virulence factors, which allow to enter and survive in several nonphagocytic cells. After cellular internalization, listeriolysin O (LLO) and two phospholipases mediate the escape of the bacterium from the endocytic vesicle into the cytoplasm, where the microorganism divides and submits the F-actin based on mobility to spread from cell to cell. The LLO (coded by the gene *hly*) is a cholesterol-dependent toxin; it is able to form pores in the membrane of phagosomes, allowing *L. monocytogenes* to escape from primary and secondary vacuoles. The cytolytic activity of LLO increases with the action of a phosphatidylinositol phospholipase C (PI-PLC), the substrate of which is phosphatidylinositol; and a phosphatidylcholine phospholipase C (PC-PLC), which is a lecithinase with enzymatic activity over phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine. PC-PLC is expressed as a protoenzyme and zinc-dependent metalloprotease Mpl is required for its maturation; so once free in the cytosol, the bacterium acquires the necessary nutrients for intracellular multiplication. Some studies have shown that LLO is a critical invasion factor, which perforates the plasma membrane of the host cell to activate the internalization of the bacterium in human hepatocytes. Moreover, other studies have shown that LLO fails to mediate the intracellular survival of *L. monocytogenes* in neutrophils, where early degranulation leads to the release of proteases such as matrix metalloproteinase (MMP)-8, degrading LLO and avoiding the perforation of the membranes [84–86].

L. monocytogenes causes a severe infection known as listeriosis, which is usually acquired after the intake of food contaminated with the microorganism. The disease mainly affects pregnant women, newborns, the elderly, and immunocompromised people, so it is rare for the disease to occur outside the aforementioned groups. Listeriosis is a mild disease in pregnant women, but it is severe in fetus and newborns. People over 65 years of age or immunosuppressed people can develop infection in the bloodstream (sepsis) or in the brain (meningitis or encephalitis). Sometimes the infection can affect bones, joints, thorax, and abdomen. Listeriosis can cause fever and diarrhea similar to that caused by other foodborne microorganisms and is rarely diagnosed. Pregnant women with listeriosis have fever, fatigue, and muscle pain (flu-like symptoms). During pregnancy, the organism can cause miscarriage, stillbirth, premature labor, and infection in the newborn. In the other risk groups, the symptoms are headaches, neck stiffness, confusion, loss of balance, seizures, fever and muscle pain. People with invasive listeriosis usually develop symptoms from 1 to 4 weeks after ingesting food contaminated with the bacterium; although symptoms have been reported after 70 days of exposure or on

the same day of the poisoning. The disease is usually diagnosed by culturing the bacterium from tissues or fluids such as blood, cerebrospinal fluid, or placenta. From food products, this microorganism can be detected by various methods such as the use of chromogenic media; immunological methods, although some are nonspecific; molecular methods (hybridization, PCR, and real-time PCR); microarrays or biosensors; and also specific commercial methods. The detection of the *plcA* virulence gene coding for PI-PLC is generally employed to differentiate hemolytic and nonhemolytic strains. Pathogenic and nonpathogenic *Listeria* species can be differentiated by their activities of hemolysin or PI-PLC [87, 88].

L. monocytogenes is a microorganism that can be present in many food products, mainly in dairy products, soft cheeses, cheeses made with unpasteurized milk, celery, cabbage, ice cream, hot dogs, and processed meats [87].

Infection with *L. monocytogenes* can be treated with antibiotics such as ampicillin, although penicillin is more effective. Some experts recommend the use of gentamicin in people with impaired immunity, including neonates, and in cases of meningitis and endocarditis. Ampicillin is only used in pregnant women with isolated listerial bacteremia. Other antibiotics that can be used are trimethoprim-sulfamethoxazole and vancomycin. Cephalosporins should not be used to treat listeriosis because they are ineffective against the microorganism [89, 90].

The general guidelines to prevent listeriosis are similar to those recommended for other foodborne pathogens. For people at high risk, it is recommended not to consume soft cheeses such as Feta, Brie and Camembert, blue cheeses, or Mexican style cheeses (white cheese, fresh cheese, or panela cheese) unless they are made with pasteurized milk; it is also recommended not to consume smoked seafood, *pâté* or refrigerated meat spreads, hot dogs, processed meats or cold cuts, unless they have been reheated at high temperatures; these are just some of the food products that people at high risk should avoid [91].

4. Strategies for disease prevention

Multiple factors associated with the procurement, handling, and food preparation contribute to an increase in the likelihood of contamination, and consequently, consumer's poisoning. Due to the importance of foodborne diseases, the number of cases presented and their severity, it is necessary to know those measures that help preventing or avoiding them; or getting a disease caused by food poisoning related to bacterial toxins [92–94].

Toxigenic microorganisms arrive to food products by cross-contamination; they come from the environment or they belong to the normal microbiota, in the case of animals. Once the contaminated food is ingested and reaches the intestines, the microorganisms get established, colonize, and, if the strain is toxigenic, produce the toxins responsible for the damage. Likewise, an incubation process must occur prior to the first symptoms. To prevent the occurrence of such diseases, health care measures, especially hand hygiene of food handlers, should be carried out; in that way, all food sectors such as restaurants, manufacturing, and distribution companies, pay special attention to hygiene measures for food handling to prevent

food handlers from inoculating the bacteria they carry on the skin on their hands. Along with other measures, they must ensure food safety, and for this, food sectors will establish policies and activities to ensure maximum quality and food safety throughout the food chain (from procurement and production to consumption) [92, 95–98].

Some of these standards are described and taken care by the *Codex Alimentarius*, which, together with the World Health Organization and the Food and Agriculture Organization of the United Nations, has the responsibility to develop and standardize the international food standards. Their objective is to ensure the quality of food products and to protect human health, as well as the correct and fair implementation of these standards. The standards of the *Codex Alimentarius* apply to processed, semiprocessed, or raw food products. In addition to all the factors used in food processing, food quality standards seek to ensure that food products are produced in hygienic conditions, and that they preserve their nutritional quality. The main standards include microbiological processes, regarding the use of food additives, pesticide use and pest control, as well as, the permissible limits of drugs or hormones used in animal production [66, 99–103].

For proper handling of food products, facilities, materials, instruments, and equipment must be kept accessible for the cleaning and disinfection process, in order to prevent food contamination by toxigenic bacteria. Cleaning procedures will include the effective removal of food residues or other contaminants; these procedures must be continuous, because some microorganisms have the ability to settle on these surfaces and to survive in adverse conditions by forming biofilm, thus, cleaning with soap and water is not enough. The methods can be chemical, with alkaline and acidic detergents; and physical, with heat, turbulent washes, or vacuum washes. Moreover, brushes or sponges can be used to remove dirt; however, the correct method of use must be considered to ensure efficiency, as well as, not using the same cleaning instrument in areas of processed and unprocessed food. Detergents or disinfectant substances should be used under the conditions proposed by the manufacturer regarding the concentration and time of action, which will depend on the type of surface and the product's presentation (liquid, solid, or semisolid). Such cleaning processes will be subject to regular monitoring and quality control, registering the areas that were cleaned and the person responsible for the cleaning. The cleaning method will be used depending on what is intended to be cleaned; in the case of smooth surfaces, the use of disinfectant and sponges or brushes to remove residues will be enough; this is done *in situ*, contrary to those dismantled equipment that require to be cleaned piece by piece. All of the above related to the establishment's cleaning must be submitted in writing to the personnel responsible for this task for the correct and efficient implementation of cleaning methods [98, 104–106].

Another important aspect in this sector is pest control. A variety of pests lurk at sites where food is produced; special care must be taken because in most cases these pests act as vehicles for toxigenic bacteria and other pathogens, endangering the consumer's health. The most common pests are rodents, flies, and cockroaches. To prevent the presence of pests, food facilities should avoid air vents and cracks; regarding food products, these should be stored in high places, inside sealed containers or bags to prevent rodents from smelling the food. For pest control, insect monitoring should be carried out on a continuous basis, through catch

patches that may contain pheromones to attract insects, electric lamps against flying insects, among others. Of all insects, flies are the most common pest in food establishments, and they are an important source of disease transmission to food and other forms of food poisoning. It is important that food establishments eradicate flies pest to avoid any contamination of food products, in restaurants, kitchens, and other establishments where food is prepared; adhesive traps can be employed. Traps are used when managing rodent pests; however, an exhaustive planning must be done to determine the number of traps to be placed, as well as location; pest prevention include specifics such as covering air vents, avoiding cracks, and storage of food in high places, inside sealed containers or in bags to prevent rodents from smelling the food. At this point, the cleaning of the workplaces is of high importance, mainly the kitchen and the surfaces that are in contact with food, to ensure quality and food safety [87, 107, 108].

Food safety is a human right and an obligation of all the governments to ensure it; it refers to the preserved quality of food products without organoleptic alterations, the presence of chemical, physical, or biological pathogens, or other undesirable alterations in the products that may affect the consumer's health. In order to ensure this characteristic, good practices must be put into operation; identification and control of the potential sources of contamination by the establishment, proper storage of food by separating raw food from processed food, and handling of food products depending on their origin (animal or vegetable). Proper waste management and drainage installation need to be taken into account. Regarding the design and equipment distribution, and the areas where the food is prepared, raw food should be separated, and previously processed food should not be exposed in the same surface. Staff restrooms must be distant from food preparation areas to avoid fecal contamination. The use of suitable uniforms and footwear, air quality, ventilation, and temperature control are essential for a working environment that allows a good development of food processing, and reduces, as much as possible, food poisoning by toxigenic bacteria [101, 109].

The Hazard Analysis and Critical Control Point (HACCP) system can be an efficient and systematic alternative to prevent toxico-infection; its function is to identify specific hazards and develop control measures to solve them, guaranteeing food safety by seven basic principles: identifying hazards and preventive measures, identifying critical control points, establishing limits, monitoring critical control points, using corrective measures, verifying processes, and registering the applied processes [63, 110].

As a preventive measure to avoid food contamination and foodborne diseases, World Health Organization (WHO) proposes the five keys for food safety [94].

- **Keep clean:** It refers to washing hands before and during food preparation; after going to the toilet; washing and sanitizing surfaces and equipment for food preparation, and to keep them away from insects and animals.
- **Separate raw and cooked food:** Prepare in different surfaces raw and cooked food and use different equipment for each type of food.
- **Cook thoroughly:** Food cooked thoroughly allow the removal of bacteria and other pathogens; toxins produced by bacteria and pathogens can also be destroyed.

- Keep food at safe temperatures: Do not leave cooked food at room temperature for more than 2 h to avoid bacteria proliferation, and try not to store frozen food for long periods of time.
- Use safe water and raw materials: Safe treated water must be used when preparing food; use fresh food products and wash adequately. Pre-processed products such as pasteurized milk, should be used as directed and not be used beyond their expiry dates.

5. Research

The field of research about bacterial toxins is very wide; the determination of the toxins structure and function has allowed the development of biotechnological applications such as the development of antimicrobial drugs, anti-cancer therapy, and vaccine creation.

Almost all projects focus on the research of vaccines containing portions of attenuated toxin, in order to protect the patient against the effects of the disease. A study carried out by Secore *et al.*, in 2017, showed the efficiency of the trivalent vaccine against *C. difficile*, which causes nosocomial infections; this vaccine contains TcdA- and TcdB-attenuated toxins and toxin components CDTa and CDTb. This vaccine showed greater efficiency in golden hamsters and in Rhesus monkeys compared to vaccines containing only the TcdA and TcdB antigens. In the case of the botulinum neurotoxin (BoNT), it is known to be of use in the treatment of muscle atrophies, mainly in facial paralysis, muscular hyperactivity, and dystonias. The BoNT has also been used to prevent facial wrinkles. However, it was found to have a preventive effect on headaches, as it is able to lessen it in some diseases such as neuropathic pain, low back pain, myofascial pain, and bladder pain. Studies supporting this statement have been carried out with studies based on human pain, these studies have shown positive and negative results. They are double-blind studies with placebo control. The positive action of the Botulinum toxin (BTX) has been characterized when administered to cells previously exposed to cigarette smoke; this suggests that it is a preventive agent to reduce the risk of necrosis in the respiratory tissue of patients who smoke [111–113].

Another notable example of toxin research is the use of toxins for medical treatments. For example, in studies by Lai *et al.*, they found that the *C. jejuni* distal cytolethal toxin can be incorporated to the lipid rafts on the membrane with the Cj-CdtA/CdtC subunit; the Cj-CdtB subunit goes through the cell membrane, it translocates to the interior of the cell and reaches the nucleus. This is an advantage that can be used to create drugs paired with the attenuated toxin or to a part of it, so that it can be able to reach the nucleus, be separated from the drug, and act as therapy against cancer, without the toxin causing any damage. Several *in vivo* and *in vitro* studies will be needed to establish it as an alternative cancer therapy [114].

The mechanisms that develop in the pathway that creates the pore have been revealed in the study of pore-forming toxins (PFT) in the cell membrane. Nowadays, the mechanism of formation is almost completely known stage by stage. The challenge in the research is to know the process in detail and, from that, design therapies with antibodies, drugs, or other

compounds that can inhibit its effects to know how the cell senses the presence of the pore, if it is at a concentration level of ions or by cytoplasmic signals, allowing it to run repair mechanisms of membrane damage [115].

An interesting group of toxins are the immunotoxins, which are formed by a portion of antibody and a portion of toxin; the toxin has an intracellular action to kill the target cells. Most immunotoxins are designed to attack cancer cells; therefore, they are alternative to chemotherapy. The regulation of immunological signals and the treatment against viral and parasite infections are also applications of immunotoxins. Nevertheless, studies should focus on the methods for obtaining the toxin-antibody compounds, because molecular cloning to obtain a hybrid immunotoxin has not been efficient. Therefore, the methods for obtaining and purifying must be improved. The recent results are the creation of smaller immunotoxins with less immunogenicity, leaving only the site of action with the membrane, or the immunogenic site allowing its insertion into the target cell. Related studies are based on the creation and purification of monoclonal antibodies against toxins; for example, the use of an optimized anti-Alpha-toxin antibody of *S. aureus* causing pneumonia. This study showed a decrease in the number of bacteria in lungs and kidneys of the evaluated mice; mice showed minimal swelling and intact lung tissue. Thus, the mice had a higher percentage of survival, even with the combined treatment of the anti-Alpha-toxin antibody plus vancomycin or linezolid [95, 116].

Another alternative is the use of chemicals that inhibit the effect of bacterial toxins. A large number of research papers have been looking for substances that may inhibit the effect of bacterial toxins in human tissue; for example, the use of Bi^{3+} ion to prevent or treat the hemolytic uremic syndrome caused by *E. coli* producing shiga toxin; this ion can be applied to animals and humans. Due to the importance of toxins in the food area, with clinical and pathological consequences, these mechanisms of action and the nature of toxins should be thoroughly investigated, in order to design strategies to prevent and manage effectively toxicoinfections [117].

It should be of particular attention, the use of toxins as an alternative treatment that allows to have tools for treating diseases such as cancer, the use of immunotoxins and pharmacotoxins.

6. Conclusions

Governments should raise food safety as a public health priority, by establishing effective food safety systems to ensure that food producers and suppliers, throughout the food chain, act responsibly and provide safe food to consumers.

Food contamination can occur at any stage of the manufacturing or distribution process, although the responsibility lies primarily with the producers. Nevertheless, a large part of the foodborne diseases are caused by food that has been improperly prepared or handled at home, in food establishments, or in street markets.

It is a joint responsibility for consumers, traders, and governments to work together to implement regulations, enforce laws that support, increase, and sustain food safety.

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