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SUDAN UNIVERSITY OF SCIENCE AND TECHNOLOGY

COLLEGE OF GRADUATE STUDIES

Prevalence of Antibiotics Residues in Meat and Application of (HACCP) in Khartoum State

إنتشار متبقيات المضادات الحيوية في اللحوم وتطبيق تحليل المخاطر ونقاط التحكم الحرجة في ولاية الخرطوم

By

Mohamed Ismail Mohamed Fangama

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Supervisor: Prof. Dr. Mohamed Abdelsalam Abdalla

Department of Preventive Medicine and Public Health, College of Veterinary Medicine, Sudan University of Science and Technology

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Initiation

عن ابن مسعود رضي الله عنه قال: سمعت النَّبي صلى الله عليه وسلم يقول: ((لا حسد إلا في إثنتين: رجل آتاه الله مالاً، فسلطه على هلكته في الحق، ورجل آتاه الله حكمة، فهو يقضي بها ويعلِّمها)).

رواه الشيخان

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DEDICATION

TO:

MY MOTHER FOR HER PRAYER AND ENCOURAGEMENT. -

MY FATHER PROF. ISMAIL MOHAMED FANGAMA, FOR HIS PRAYING, -
CARE, SUPPORTING, ENCOURAGEMENT, FOLLOW- UP, HELPING AND
ADVISING.

MY WIFE DR. EMAN ABDELWAHAB, FOR ALL HER SUPPORT AND -
HELPING TO COLLECT THE SAMPLES, HER UNDERSTANDING AND
PATIENT.

MY AUNT (HAWA), FOR PRAYING AND SUPPORTING. -

IN ADDITION, I DEDICATE THIS WORK TO: MY KIDS AND TO ALL MY -
BROTHERS AND SISTERS

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Abstract

The research was conducted in Almoilih and Albaraka slaughterhouses in Karary Locality, Khartoum State (The research title is Prevalence of antibiotics residues in meat of cattle, sheep, goats and processed meat in Khartoum State in order to assess the level of hazard). The objective of this study was to detect antibiotic residues in raw bovine, ovine, caprine and processed meat to examine the occurrence of antibiotic residues by using bacterial test, in order to determine the prevalence and incidence of antibiotics residues and evaluate the risk level, so as to provide the suitable solutions for the chemical hazards. The main problem of this study is the lack of knowledge and ineffective diagnosis of food borne diseases and poor reporting systems of relevant authorities within health institutions. The samples were collected from different animals. From each animal samples from (liver, Kidney and Muscles), were taken in addition samples from (Lung and Hearts) of bovine. The samples were tasted in the College of Veterinary Medicine, Bacteriology laboratory, Sudan University of Science and Technology, Helaat KuKu. One plate screening tests (O.P.I) were done by using samples taken to microbiology laboratory. Microbial inhibition one plate of *Bacillus subtilis* in agar medium was used. The results obtained for Bovine, Caprine, Ovine and processed meat were as follows: 46.4%, 12.5%, 96.4% and 27.3% respectively as positive samples, and the percentage of the result for the organs tested, kidney, liver, heart, muscle and lung were 85.3%, 85.3%, and 48%, 100% and 48% respectively. Also a questionnaire was designed and distributed to the veterinarians and the data were analyzed statistically by Social Package of Scientific System by SPSS software 24 package. The result showed that, 60% of Veterinarians give tips to the owners about the withdrawal period and 60% did not adhere to dosage in the prescription. Also 92% of antibiotics administration and follow-up is carried out by the owners

and workers. Only 20% only of the owners adhere to the guidelines, and 92% of the veterinarians did not continue the treatment by them self. The Oxytetracycline group, represented about 72% of antibiotics groups used for the animal's treatment. The study recommended that the authority should ensure compliance with the related agencies to avoid the misuse of antibiotics and routine drug residues surveillance program should be established in the country to ensure food safety.

الملخص

أجريت الدراسة بمذبحى المويلح والبركة في محلية كرري ولاية الخرطوم. بعنوان إنتشار رسوبيات المضادات الحيوية في اللحوم و تطبيق تحليل المخاطر نقاط التحكم الحرجة. هدفت الدراسة إلى التعرف علي حالة رسوبيات المضادات الحيوية في لحوم كل من الأبقار والضأن والماعز و اللحوم المصنعة في ولاية الخرطوم. مشكلة الدراسة تتمثل في نقص المعلومات وعدم توفر الإختبارات الفعالة لتشخيص الأمراض المتولدة غذائيا وضعف نظام التقارير لدى السلطات ذات الصلة داخل المؤسسات الصحية . وللحصول على المعلومات تم أخذ عدد 75 عينة من حيوانات مختلفة من مسلخى (المويلح و البركة) ومن كل حيوان تم سحب عينات من الأعضاء (الكبد –الكلي– العضلات) وفي الأبقار تم إضافة (الرئة و القلب) إلى العينات . إتبعت الدراسة المنهج الوصفي و فحص الطبق الواحد البكتيري.أما الطرق التي استخدمت لجمع المعلومات تتضمن تحليل عينات اللحوم والإستبانة ، والمقابلات الرسمية وغير الرسمية والملاحظة. تم اختبار العينات بمعمل كلية الطب البيطري بجامعة السودان للعلوم والتكنلوجيا بحلة كوكو بالخرطوم بحري. وتم تحليل الإستبانة ببرنامج التحليل الإحصائي العلمي (SPSS) الإصدار 24. أهم النتائج توضح أن عينات كل من الأبقار والماعز ولضأن واللحوم المصنعة يتمثل الموجب منها بالنسب46.4 % ,12.5%,96.4% و 27.3 % على التوالي.أما الأعضاء الكلي والكبدوالقلب والعضلات والرئة كانت بالنسب 85.3% ,85.3%,48%,100% و 48%. على التوالي.كانت أهم نتائج الإستبانة أن 60% من الأطباء البيطريين يقدمون الإرشادات الخاصة بفترات سحب المضادات الحيوية لاصحاب الحيوانات وأن(60%)لا يتقيدون بالجرعات المذكورة في الوصفة الطبية ،كما أن 92% من أصحاب الحيوانات وعمال المزارع يقومون بمتابعة حقن المضادات الحيوية علماً بأن 20% فقط من أصحاب

الحيوانات يتبعون الإرشادات البيطرية,تبين أن أكثر مضاد حيوي مستخدم هو مجموعة الأوكسيتتراسيكلين إذ يمثل 72% من الإستخدام . توصي الدراسة الجهات الصحية ذات الصلة بتشديد الرقابة علي الإستخدام السيىء للمضادات الحيوية مع القيام بمسوحات للتقصي عن رسوبيات المضادات الحيوية لضمان سلامة الغذاء.

ABBREVIATIONS:

ADI: Acceptable Daily Intake associated with the food under consideration to decide which are cause illness or injury in the absence of its control" (FDA, 2009).

CCP Critical Control Point: (Food safety) step at which control can be applied and is essential to prevent or eliminate a food safety hazard or reduce it to an acceptable level (ISO22000:2005).

CCP: Critical control point means a step at which control can be applied and is essential to prevent or eliminate a food safety hazard or reduce it to an acceptable level.

Corrective Action: Critical limit means a criterion which separates acceptability from unacceptability.

CVMP: Committee for Veterinary Medicinal Products

DDT: Dichlorodiphenyltrichloroethane

EU: European Union

FAO: Food and Agriculture Organization

FBD: Food Borne Disease

FDA: Food and Drug Administration

Food Chain: Sequence of the stages and operations involved in the production,

Food poisoning: Illness that results from the ingestion of bacteria, their toxins or viruses, which may be present in food (Barrie 1996).

Food Safety Hazard: Biological, chemical or physical agent in food, or condition of food, with food safety hazards" (FDA, 2009).

Food Safety Management System (FSMS):

Food safety objective: means the expected food safety outcome for the product as a result of implementing the HACCP plan. It may have a qualitative or quantitative association with a level of risk to the consumer.

Food Safety Policy: overall: Intentions and direction of an organization related to food safety as formally expressed by top management (ISO22000:2005).

Food safety: "The concept that food will not cause harm to the consumer when it is prepared and/or eaten according to its intended use.

GFSI: Global Food Safety Initiative

GMP: means good manufacturing practice.

HACCP audit: means a systematic and independent examination of an applied HACCP plan to determine whether activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are achieving set objectives on an ongoing basis.

HACCP co-coordinator: is an appropriately trained person responsible for coordinating the application and implementation of HACCP at a premise.

HACCP plan :is a document prepared in accordance with the principles of HACCP analysis to ensure the control of hazards which are significant for food safety in the segment of the food chain under consideration.

HACCP: Hazards Analysis Critical Control Points

Hazard analysis critical control point (HACCP): is a system which identifies, evaluates and controls hazards which are significant for food safety.

Hazard analysis: is the process of collecting and evaluating information on hazards and conditions leading to their presence to decide which are significant for food safety and therefore should be addressed in the HACCP plan.

Hazard: means a biological, chemical or physical agent or condition with the potential to cause an adverse health effect.

Input: means incoming materials such as consumable or non-consumable items added to the product during the process. Consumable items include raw materials, ingredients and food additives. Non-consumable items include wrapping, packaging and containers.

Is a network of interrelated elements that combine to ensure that food does not cause adverse human health effects, these elements include programs, plans, policies, procedures, practices, processes, goals, objectives, methods, controls, roles, responsibilities, relationships, documents, records and resources (ISO 22000:2005)?

ISO 22000: ISO 22000:2005 specifies requirements for a FSMS where an organization in the food chain needs to demonstrate its ability to control food safety hazards in order to ensure that food is safe at the time of human consumption (ISO, 2005).

ISO 9001: Sets out the criteria for a quality management system, is based on a number of quality management principles including customer focus, motivation and implication of top management, the process approach and continual improvement**ISO**: is the International Organization for Standardization.

JECFA: The Joint FAO/WHO Expert Committee on Food Additives

likelihood of introducing food safety hazards to and/or the contamination

Monitor: means the act of conducting a planned sequence of observations or measurements of control parameters to assess whether a CCP is under control.

MRL: Maximum Residue Limi**t**

Operational PRP Operational Prerequisite Program:

or proliferation of food safety hazards in the product(s) or in the organization (ISO22000:2005). prepared and/or eaten according to its intended use (ISO22000: 2005).

Prerequisite programme: is a documented programme covering an activity which may interact within and across various processes and which has the potential to influence the food safety outcome. It may also be referred to in other documents as good hygienic practices, good manufacturing practices, standard operating procedures, umbrella programmes or satellite programmes.

PRP identified by the hazard analysis as essential in order to control the

PRP prerequisite program: (food safety) basic conditions and activities that are necessary to maintain a hygienic environment throughout the food chain suitable for the Production, handling and provision of safe end products and safe food for human consumption(ISO22000:2005).

Quality Management System (QMS):

Requirements have been fulfilled [ISO 9000:2000, definition 3.8.4].

Revalidation: means a reconfirmation that the HACCP plan is complete and can deliver the expected food safety outcomes after changes (modification) have taken place.

Risk: means a function of the likelihood and severity of an adverse health effect on the consumer as a result of exposure to a hazard.

SANA: South African National Standard Significant and must be addressed in the HACCP plan" (FDA, 2009).

SOP: means standard operating procedure.

Step: is a point, procedure, operation or stage in the food chain, including raw materials, from primary production to final consumption.

Task description: is a description of the expected operational activities at a process step. Examples of presentation include a written description, photos or a video presentation. This may also be known as a job description or work instruction.

TQM: means total quality management.

Validation of HACCP: plan means initial confirmation that the HACCP plan is complete and can deliver the expected food safety outcomes

VMP: veterinary medicinal products

WHO: World Health Organization

INTRODUCTION

Hazards analysis critical control points (HACCP) used to be developed as an administration tool to provide a greater structured approach to manipulate identified hazards and its comprehensive food, safety-monitoring system designed to stop risks from developing alongside the production process, therefore ensuring an excessive degree of food security (Bjerklie, 1992; Karr, *et al*, 1994). More recently, HACCP has been used in the meat of animals, poultry, seafood, juice and egg industries. Now, the Food and Drug Administration (FDA) of (USA) is considering developing regulations for the dairy industry too (Riswadkar, 2000; Bardic, 2001).

The use of antimicrobials for the cure or prevention of disease in animals closely follow their uses in humans (Gustafson, 1993) and it could be administered through injections (intravenously, intramuscularly, or subcutaneously), orally in feed or water, topically on the skin and by intramammary and intrauterine infusions (Mitchell *et al*., 1998).

The most probable reason of violative drug residues is the failure to observe withdrawal instances (Paige and Kent, 1987; van Dresser and Wilke, 1989; Guest and Paige, 1991; Paige, 1994). Improper upkeep of treatment records or failure to identify treated animals accurately may also lead to their omission (Sundlof, 1989), improper use of a licensed product or through the unlawful use of an unlicensed substance. Extra-label dosages and use of drugs which have not been authorized for the species in the query might also lead to violative residues (Papich *et al*., 1993; Kaneene and Miller, 1997; Higgins *et al*., 1999).

The Harmful outcomes of antimicrobial residues in meals of animal origin may additionally cause many problems same as toxic effects, results on intestinal

macrobiotic, immune system are important (Gorbach, 1993; Waltner-Toews and McEwen, 1994; Perrin-Guyomard *et al*., 2001). The Antimicrobial drug residues in animal tissues might also cause hypersensitivity reactions in humans. (Dewdney *et al*., 1991; Sundlof *et al*., 2000).

Once the process of safety evaluation is complete and MRLs (Maximum Residue Limit) have been derived for a substance, consideration is given to the probable level of residue which might also be expected to remain after the use of the substance in accordance with good veterinary practice, and to the availability of analytical detection methods appropriate for use for activities monitoring purposes. The MRLs may be further reduced to take account of these factors (EC, 2001).

A simpler method consists of declaring the withdrawal time as the time in which the residues in all tissues of all discovered animals have fallen beneath the respective MRLs (Concordet and Toutain, 1997). Bayesian methods have also been proposed to derive inferences on the parameters of interest (Fisch, 2000).

In 1970 a microbiological check for each detection and identification of antimicrobials in meat was described (van Schothorst and Peelen-Knol, 1970).

A screening approach is the first-hand analysis of the sample to establish the presence or absence of residues (Aerts *et al*., 1995). Physico-chemical methods are specific and quantitative however they can also be time-consuming if the identity of the antimicrobial being sought is not recognized before work begins. Therefore, a post-screening test is needed for the preliminary characterization of the residue (Lott *et al*., 1985; Aureli *et al*.,1996; Ferrini *et al*., 1997).

3. Research objectives:

Objectives of the research are to:

1- To determine the prevalence and incidence of antibiotics residues in Khartoum state to evaluate the risk level and provide the suitable solution for the chemical hazards.
2- To provide up to date information concerning the prevalence of antibiotics residues in Sudan.
3- To get a real data about the veterinarian's awareness, biosecurity, knowledge of residuce (harmfulness and randomly uses).

CHAPTER ONE

LITERATURE REVIEW

1. Food safety legalization:

The food safety is used to make the production, processing, distribution, preparation, marketing, access, consumption, and disposal. These strategies want resources such as people, businesses, farms, communities, interventions, policies, and politics in one manner and coordination for a company to make growth (Miljöstyrningsrådet, 2007). A food safety standard helps to coordinate this via guidance and examples and see to that the distribution channels are run according to current legislation and regulations. According to the Swedish Board of Agriculture, Sweden has elevated the export of commodities from agriculture and food industry in the latest years (Jordbruksverket, 2011). The food safety policies have existed for a long time, already in the Pentateuch decrees (Moseböckerna) arrangements regarding hygienic factors have been recorded (Ågren, 1991).

Slaughter of animals for food was supposed to be carried out in public slaughterhouses and managed through remarkable incidents. Following this, a public health act was once published both in 1874 and in 1919. It managed the common handling of food, food premises, and policies for certain goods, such as meat, milk, fish, and eggs. All Previous food charters were changed by means of rules from 1951 accompanied via the present Swedish food legislation that came in 1972. The Swedish National Food Administration was also established in 1972. According to Ågren (1991), the food legislation has two major purposes, which are to protect consumers from hygienic and economic hazards.

The quality of food is based on the product safety, and to ensure this, producers have to work according to the HACCP-system (Hazard Analysis Critical

Control Point).

HACCP is an internationally recognized management system developed by way of NASA and is used in food production to remove hazard for the duration of food manufacturing (Mårdén, 1995).

The expectations of the food industry from consumers and authorities have improved over the previous years (Bergström and Hellqvist, 2004). This improvement has led to the use of global standards related to quality supervision through manufactures.

A standard provides a method of preventing problems and disaster and it can additionally assist to manage necessities from authorities, the market and others. The major purpose of a food safety standard is to provide consumers with secure food (Lusk *et al*., 2011). The standards BRC, ISO 22000 and IFS are extensively used and properly recognized. These standards include HACCP, high-quality supervision as well as GMP (Good Manufacturing Practices).

1.1 The British Retail Consortium (BRC):

It was created a standard designed for British food shops and for different producers producing food for the British market (Miljöstyrningsrådet, 2007). The name of the standard is the BRC Global Standard for Food Safety, similarly referred to as the BRC standard, and the motive of it is to obtain secure food products and service for the consumer. The BRC standard is a technical standard based totally on HACCP and it includes distinct law related to production, product management and traceability (BRC Global Standards, 2011) and it was developed in 1998 as a result of the industries need for a safety evaluation system concerning the security of retailer's private label products.

The BRC preferred is in most cases used in Great Britain and in the countries of Scandinavia (Aranea, 2011).

1.1.1 Uses:

1-The reason was once to assist brand owners and retailers to produce reliable, safe food products of high quality.

2-To help the manufacturer owners and retailers with due diligence defense in case of a prosecution by using enforcement authorities, since retailers and manufacturer owners have a legal responsibility for their brands beneath the EU food law (Bergström and Hellqvist, 2004).

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1.1.2 Advantages:

The important benefit is the improved relation to other manufacturers and companies, no longer so a great deal the relation to buyers and customers. The certificates will assist the commercial enterprise to keep its clients when the certification is a requirement for making business. According to Bergström and Hellqvist (2004), it also helps the manufacturer or company to create new opportunities, to get into new markets and start producing for new consumers. Its leads to an increased trust among clients and will ensure the communication to authorities that may have not been the case as a certificated business.

1.2 Standardization Literature

At first glance, the history of standards seems to have had greater currency in other disciplines, especially in the history of technology, however, it has come to be a famous theme in histories of biomedicine and public health (Palgrave, 2010). Many historians Slaton and Abbate, (2001) do no longer explicitly talk about a standard without additionally referring to its technique of development; that is, the

concept of a standard as a fixed ultimate product is inextricably bound up with the procedure through which it is attained. Or the extra pertinent query to ask is: what are the targets or effects of standards and standardization? Drawing upon definitions and methods that have been at the beginning employed mostly by using historians of technology, however, have additionally been adopted via historians who check out biological or biomedical standards, these objectives include:

(1) To neutralize, objectify knowledge; to make matters uniform; it is a way of 'making things the same' (to borrow from the historian of technology Ken Alder);

(2) To make knowledge and products more portable from the local setting to the global; standards permit for popular application, for example shifting information from the laboratory to the outdoor world (Latour, 1999).

(3) To mitigate risks such as injury to health.

(4) To allow collaboration amongst communities, countries, or laboratories, because, as Pieters has remarked, for pragmatic reasons "matching nature is now not as necessary as matching different laboratories" (O'Connell, 1993).

Thus, this intention of producing functionally equal artifacts ideally should equalize power distribution and create a level playing field for these with pursuits in the product; alternatively, some historians of technology and industry have advised that in some cases the opposite occurs. The process has inherent social, political and economic biases, and outcomes in struggles of authority and struggle when attempting to reach consensus. For example, Ken Alder shows how in late 18thCentury France the standardization of interchangeable parts for Napoleon's weapons by military-engineers happened at the cost of marginalizing local artisans and craftsmen, effectively-subordinating their knowledge to an extra centralized authority (Alder, 1998).

Slaton and Abbate (2001) additionally presents the concept that the lives of standards are "hidden" or invisible, that there is an excellent deal of work that goes on behind the scenes before the last product is available for use, application or consumption. Standards are thinking to be "instruments of reduction: reducing complexity and variety in products and processes, decreasing costs, reducing the time and effort for efficient industrial operation. But ultimately, they argue that standards effectively add complexity, bring economic control and serve as mediums of exchange and negotiation. Standards are dynamic and not necessarily secure entities or uniform when thinking about their effects. So, following up on some of these topics and approaches, and employing the idiom of coproduction. There are "stories behind the standards": they are cultural artifacts of the entire process, they embody all of the knowledge that goes in to their development, and they are symbols of scientific expertise, and authority, national and economic interests. They can be an end result of a political, economic, epistemological, cultural or ideological conflict or dialogue when one standard is created or adopted over another (Lampland and Star, 2009).

Bearing this in mind, the role of scientific standards inside a distinctly politicized and financial environment such as Codex is intriguing.

The Codex Alimentarius used to be thrust into the limelight in the mid-1990s when high-profile health concerns, import bans, and court instances started to surface as a result of the use of increase promoting hormones in beef, as well as the rise of production aids such as the milk hormone.

Bovine Somatotropin (BST). Debates over maximum residue limits (MRLs) for these materials frequently pitted countries like the U.S. against the European Union and forced the Codex to think about whether to base its decisions strictly on sound

science or consider "other limiting factors" such as patron concerns, animal welfare, fraudulent or unfair trading practices, labelling and other moral and cultural considerations. (Jukes, 2000).

One recent find out about of the Codex described that it functioned like a sort of "gentlemen's club" in its early years, earlier than its entanglement with the WTO (Veggeland and Borgen , 2002) This was once a self-referential observation made by way of a Codex member and this phrase was once also picked up and used in an empirical study of Codex, one that attempted to assess its institutional values and culture. These researchers observed the Codex conferences and suggested that earlier than it linked up with the WTO, Codex focused extra on technical discussions and there had been fewer politically or economically motivated obstructions; that is, no matter its politicized environment, disagreements over standards rarely arose or impeded the work of the committees. Furthermore, this phrase conjures up images of a friendly, diplomatic setting, with polite correspondence, and networks of professionals all acting in cooperation as standards are developed.

1.3 **History of food safety:**

In 1946, representatives from 25 countries joined to create a common and unified industrial standard; the organization created was the International Organization of Standardization (ISO). ISO has posted more than 18,500 global standards in a 60-year time beginning in 1947. These standards range from agriculture and construction Standards to mechanical engineering, to state-of-the-art data technological know-how advances (ISO, 2011).

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) have played the main role in the improvement

of food safety risk analysis. In 1991, the Joint FAO/WHO Conference on Food Standards, Chemicals in Food, and Food Trade recommended that the Codex Alimentarius Commission (CAC) incorporate hazard evaluation principles into its decision-making process. The Codex Alimentarius Commission, at its 1991 and 1993 sessions, encouraged the recommendation of the Conference to base its decision on risk evaluation principles, specifically with regard to food contaminants and encouraged the use of a uniform method via the applicable Codex Committees. In 2003, the Codex Alimentarius Commission adopted Principles for Food Safety and Risk Analysis to be used in the Codex framework and initiated work on the development of food safety risk analysis principles for using by national authorities. During the final decade, considerable progress has been made in growing a framework and principles for risk analysis, which is currently being applied in several different countrywide and global settings, and similar developments are ongoing (FAO, 2009).

1.3.1**Traditional food safety systems**

FAO (2006) defined that food safety is the responsibility of absolutely everyone involved with the food chain from regulators to producers to consumers. However, governments are responsible for providing an enabling institutional and regulatory environment for food control. Most developing countries already have food management system in place, usually based on hygiene and adulteration/fraud inspection. While these vary considerably, they usually contain food legal guidelines and regulations, food control management, inspection and laboratory services, and sometimes mechanisms for information, education and communication and monitoring of the food supply.

The growing globalization of the food trade, urbanization, altering consumption patterns, the intensification of agriculture, increasing travel and tourism. New

kinds of production and manufacturing systems are just some of the trends that are having a serious impact on food safety in many countries. At the identical time, the number of existing and new food safety hazards are of increasing concern. New pathogens are also frequently emerging, and current ones evolving or re-appearing. The resistance of foodborne pathogens to antimicrobial agents for instance, of increasing concern.

Although ordinary food safety systems have been quite effective in decreasing food risks in the past, they are unable to detect and resolve many current problems. Furthermore, to effectively deal with the full range of complex, persistent pervasive and evolving challenges confronting different parts of the food chain. A current food safety system, with the new Risk Analysis approach, has the ability to diagnose more sharping the troubles and to recommend focused interventions so as to properly deal with them(FAO,2005)

1.3.2 **Importance of Food Safety**

Food safety is an international issue. Governments all over the world are working to minimize foodborne diseases and illnesses. Consumers' concerns and new food safety problems are the drivers of this heightened awareness (WHO, 2007). Knight *et al*. (2007) assessed consumers' perceptions of restaurant food safety, they found that consumers in the United States (U.S.) believed that restaurants have can produce and serving safe food yet rated restaurants as much less capable of offering safe food compared to grocery stores and producers (farmers).

In the U.S., many states require that the food service person in charge and other employees to demonstrate knowledge of food safety; even though training alone might also not be sufficient to improve food handlers safe food practices (York *et al*., 2009).

In 2010, the Center for Disease Control and Prevention (CDC) released new estimates of foodborne sickness outbreaks in the U.S. Every year, an estimated 9.4 million illnesses, 55,961 hospitalizations and 1,351 deaths too end as result from consumption of foods contaminated with recognized disease retailers (Scallan *et al*., 2011b) with an extra 38.4 million illnesses, 71,878 hospitalizations and 1,686 deaths estimated from consumption of foods contaminated with unspecified agents (Scallan *et al*., 2011a).

In the United Kingdom, it is estimated that a million human beings suffer from foodborne illnesses every year; 20,000 people are hospitalized and 500 die due to the fact of foodborne illnesses (Tam *et al.,* 2011). Gormley *et al*. (2011) mentioned a reduce in foodborne outbreaks between the years of 1992-2008 for England and Wales; however, the outbreaks linked to food provider establishments had increased. "The food service sector needs to undertake excellent control measures, and follow recommendation provided by national food agencies to decrease the danger of infection" (Gormley *et al*., 2011). Preventative measures can be taken to mitigate the dangers of foodborne illnesses and diseases.

In Africa, food safety and quality management are becoming increasingly vital at both the national and worldwide levels. Access to export markets may be limited where producers are not able to comply with global food safety requirements (for instance FAO/ WHO Codex) and these of importing countries. At the national level, improvements in meals safety and consumer health might also be hindered via the need for suitable food safety and consumer health policies, fragmented institutional systems, effective food regulation and enforcement, food producers and caterers working below unsanitary and unhygienic environments and a team of workers who have minimal education. Many African consumers might also up to now not make the link between sick health and hazardous food; an example of this

is the consumption of staple meals (e.g. cassava and maize) contaminated with high levels of mycotoxins (Webb et *al*., 2014).

According to Jabbar and Grace (2012) Food safety in South Africa is, regulated by means of a range of Acts, which include a comprehensive set of the center of attention factor or activity or function along the chain from farm to fork. A generic description of focus points at major levels of animal product supply chains.

The Food Laws in Ghana include the Food and Drugs Act PNDCL 305B of 1992 which covers food safety and handling requirements and penalties for breaking the Law. The existing Hygiene Principles are no longer legally binding (Authority, G.S 2013) however are guidelines, which the food industry can use to ensure food safety.

The government of Ghana has additionally given directives to the local authorities consisting of metropolitan assemblies and their districts to actively manipulate and screen food safety practices of food vendors who are people or crew of humans who promote ready to eat foods at readily accessible areas including caters, nightclubs, beer bars, chop bars, cold stores, hotels and restaurant operators and bagged water processors. The Water and Food Hygiene unit of the Environmental Health Department of the districts is responsible for the health monitoring and certification of food vendors, which is subject to renewal on a yearly basis. Food preparation traditionally in this U. S.A. is a woman's place and this has reflected in most demographic reports of employees in this field. Level of education (formal) which is considered to have the direct positive effect on Good Hygiene Practices is low among food handlers in Ghana (Tomlins *et al*., 2002, Ackah *et al*., 2011 and Ababio *et al*., 2012).

Hygiene practices amongst food handlers, usually food vendors and catering services have been reported to be below standard (Tomlins *et al*., 2002, Afoakwa, 2005, Addo *et al*., 2007, and Feglo and Sakyi, 2012). Research covering the hospitality industry has been around hotels, eating places and avenue food companies ordinarily in the capital city, Accra (Addo *et al*., 2007, Donkor *et al*., 2009 and Ackah *et al*., 2011). Colony Forming Units (CFU) g−1 set by way of the Ghana Standards Authority for Ready to Eat Foods (RTE) has been mentioned with the aid of Mensah *et al*. (2002) and Feglo and Sakyi (2012).

In Ethiopia, key stakeholders involved in food safety management include Ministry of Health (MoH), Ministry of Agriculture (MoA), Quality and Standards Authority of Ethiopia (QSAE), Environmental Protection Authority (EPA), Ministry of Industry (MoI), Ministry of Trade (MoT), different Federal and Regional Governmental Bodies, Research Institutions, Ministry of Education (MoE), Food Manufacturers, Food distributors and Hotels (FAO and WHO, 2005; Dawit, 2010).

Ethiopian Food, Medicines and Health Care Administration and Control Authority have been established in accordance with Food, Medicine and Health Care Administration and Control Regulation No 189/ 2002. According to the new proclamation, the Authority is responsible for assuring safety and quality of food, safety, efficacy, quality and appropriate use of medicines, competence and ethical practice of health professionals, the competence of health and health-related institution and services (Dawit, 2010). Quality and standards authority of Ethiopia (QSAE) in food safety, The Quality and Standards Authority of Ethiopia is the National Standards Body of Ethiopia established in 1970. The Authority, is below the Ministry of Science and Technology. The Authority is mandated to make sure food safety thruough certification, inspection, and testing (Erkyihun, 2010).

Pesticides have enabled farmers to produce some crops profitably in any other case unsuitable locations, extend developing seasons, preserve product quality and extend shelf life. Nevertheless, these chemical substances additionally pose some risks if used improperly or too regularly (US EPA, 2007).

According to Jabbar and Grace (2012), the ministry has drafted a wide variety of policies in 2010 to enforce the above. The regulation on prevention and control of animal's illnesses describes the methods of disease notification of livestock disease outbreaks, prevention and containment of epizootic and zoonotic disorder, animal testing, quarantine procedures, the creation of disorder free zones and containment of fish and bee diseases. The proposed policies on animal identification and motion control outline the procedures of premise (farm) registration, identification of food animals, recording and tracking of food animals. Regulations on animals, animal products and by-products describe the procedures of quarantine, vaccination, action to be taken in case of sickness prevalence and list the requirements to be met in export and import of food of animal origin.

In Kenya, the proper of citizens to safe food is enshrined in the country's constitution. A variety of countrywide policy files such as the National Recovery Strategy 2003, Strategy to Revitalize Agriculture 2005, National Livestock Policy 2007, Strategic Plan on Creation of Animal Disease Free Zones 2007, the draft National Food Safety Policy 2010, and the National Dairy Development Policy contain explicit or implied statement about assurance of safe meals for the residents (Kang'ethe, *et al*., 2011).

Self-regulation mechanisms: Processors in some of the animal products value chains are organized into member associations such as the AFIPEK, which has developed its own interior standards, slightly more stringent than the statutory

standards. The individuals are obliged to adhere to these standards creating a self-regulatory mechanism. The Kenya Dairy Processors Association (KDPA) has additionally been revived and is expected to make a contribution to self-regulation in the sector. In the red meat sector this aspect is still in the formative stages However, some other acts that have an indirect role in the safety of cattle products such as acts governing the transportation of food products, quarantine of live animals etc, might have been left out of the list. Yet it appears that there is a multiplicity of acts and implementing agencies with overlapping mandates, which demand a high degree of coordination and collaboration, however, that is frequently lacking (Kang *et al*., 2011)

In Tanzania, food safety is implied in the Agriculture Policy 1997 and the Livestock Policy 2006, the cornerstone of which is to achieve food and nutrition security for the country and commercialization of smallholder agriculture in an environmentally sustainable manner. Food safety is additionally implied in the food and diet policy for Tanzania prepared by way of the Ministry of Health in 1992 (Kurwijila *et al*., 2011). While in Ghana and Mozambique, there is not explicitly stated or approved food safety policy even though a number of government bodies are empowered through legislation or acts to deal with food safety issues (Munguambe and Hendrickx, 2011; Jabbar and Grace, 2012).

According to Jabbar and Grace (2012) Zanzibar has a few laws and regulations of its own regarding food safety and quality and consumer protection.

1.3.3 **Challenges to food safety**

Food safety challenges vary with the aid of region, due to differences in income level, diets, local conditions, and authorities' infrastructures (WHO, 2004). Here

are some trends common in both developed and growing countries that can increase food safety challenges (Rocourt *et al*., 2003).

1. Changes in animal husbandry

Modern intensive animal husbandry practices have been used to maximize production. This has resulted in the emergence and elevated prevalence of several human pathogens, like *Salmonella* and *Campylobacter*, in flocks or herds of the most vital manufacturing animals (Global and Local, 2005). Crowding of animals has led to the increased use of antibiotics on so-called "factory farms" which in flip has been linked to the emergence of new lines of antibiotic-resistant bacteria (Global and Local, 2005).

2. Increases in international trade and travel

International trade approves for the rapid transfer of microorganisms and introduction of new and unfamiliar foodborne hazard from one country to another. The elevated time between processing and consumption of food due to long distance global travels leads to additional opportunities for contamination, time /temperature abuse, and growing the hazard of foodborne sickness (WHO, 2004).

3. Changes in food or agricultural technology

Advances in processing, preservation, packaging, shipping, and storage technologies deliver new forms of foods to the market and sometimes-new hazards. For example, the accelerated use of refrigeration to lengthen the shelf life of ready-to-eat foods has contributed to the emergence of *Listeria Monocytogenes* (Rocourt *et al*., 2003).

1.3.4 **Quality management system:**

Færgemand (2008), said that the use of the same methods and ways of interpretation will make the work with systems of quality management easier. Using the same methods is extra effective and will increase food safety, maximizes the use of resources and reduces the risk of critical mistakes and misunderstandings.

According to Mårdén (1995), the most important benefit of certifying a food production is the competitive advantages. Other suppliers might also not follow a quality management system and retailers often look for suppliers with certificates.

A certification is required by the most important European outlets of suppliers included in their supply chain (Veritas, 2009).

1.3.5 **Good Manufacturing Practice (GMP) and Good Hygiene Practice (GHP):**

A management system of strategies and products is indispensable for each food producer (Mårdén, 1995). Good manufacturing practices (GMP) can be described as proper housekeeping in the meals manufacturing (Bernhardt and Raschke, 1998). GMP ensures manufacturing of safe food products with constant quality. Other advantages of the system are decreased waste and improved profits. Initially, the pointers for GMP were developed for the pharmaceutical enterprise however it used to be quickly modified to go well with the production of food too. GMP involves routines for management of production premises, uncooked material, hygiene and equipment and should be well documented and included in the company tradition (Mårdén, 1995). Well-functioning GMP´s are necessary when working according to systems such as HACCP or standards like ISO 22000 or BRC. HACCP is a system that goes deeper and similarly than GMP into the evaluation of potential dangers and how to manage them. According to Bernhardt

and Raschke (1998), it is: “essential that administration is satisfied with the need to introduce GMP. They must recognize now not only the advantages of GMP, however also appreciate the assets required to make it work.”

Only if the management is supportive and understands the importance of such a system, it will work. While GMP especially refers to the technical aspects of the production process, the focus of GHP (good hygiene practice) is on the hygiene components in food production (Buncic, 2006). The terms GMP and GHP are often used simultaneously because in food processing it is hard to consider hygiene besides considering the technical context. Both GMP and GHP are prerequisite programs needed to be implemented prior to introducing a HACCP plan. Using only GHP is now not adequate to produce high-risk food such as food of animal foundation however in the manufacturing of low-risk foods, such as cereals and grains, GHP alone is sufficient.

1.3.6 **GFSI (Global Food Safety Initiation):**

The GFSI is a foundation of giant and main companies in the retail business all over the world and one of their objectives is to benchmark standards used when certifying food production, to develop the competence and potential in food safety systems and to make them more consistent and high quality (GFSI, 2012, b).

1.3.6.1**History**

Partly due to a quantity of food safety scares before May 2000, a group of international retailer CEOs felt the need to enhance the food security and to assure higher client safety (GFSI, 2012, a). They launched the Global Food Safety Initiative below Belgian regulation in 2000.

1.3.6.2 The Main Idea of GFSI:

GFSI acknowledges several requirements worldwide, amongst them BRC, IFS, FSSC 22000 and the Dutch HACCP Standard (GFSI, 2012, a). According to GFSI, the basis used to be no longer created to set up a single standard regulating all food safety, but to encourage innovation and development of different standards, which meet a frequent foundation of requirements set up by way of GFSI. GFSI does no longer lift out any certification activity of their very own and each day management is undertaken by means of the Consumer items discussion board (GFSI, 2012, b).

1.3.6.3 An audit:

An audit is an in-depth inspection of the food producer and their facilities where they are inspected against the requirements of the food hygiene policies or a standard (Souness, 2000).

1.3.7 **ISO**

ISO, the International Organization for Standardization, is an organization modifying various standards regarding methods and systems for many different businesses (ISO, 2010). One hundred and three national standards or bodies have been participants of the ISO organization in late 2010 and ISO´s portfolio then held over 18500 standards regarding economic, environmental and socially sustainable development.

1.3.7.1 Uses

It is a quality management system addressing food security troubles in food production and can be applied to all kinds of a corporation in the food chain. According to Færgemand (2008), ISO 22000:2005, Food safety administration

systems:" aims to make certain that there are no weak hyperlinks in the food supply chain."

ISO 22000 used to be designed to healthy in different methods due to the fact that the requirements for food safety are diverse among food producers. The standard does not provide a check-list considering that processes due in one production may additionally now not be appropriate in another. ISO 22000:2005 is not recognized by means of GFSI due to the lack of technical specification for sector PRPs. In a combination with PAS 220, ISO 22000 is referred to as FSSC 22000 and is diagnosed by using GFSI.

In Sweden at least 33 companies in the food chain are certified with the aid of ISO 22000 (Modeled, 2012).

1.3.7.2 ISO 22000 in food service

The International Organization for Standardization (ISO) is a network of national standards bodies founded in 1947.ISO is the world's largest developer of voluntary international standards and have published more than 19 50 global standards overlaying all aspects of technology and business, including food safety. International standards ensure that products and services are safe, reliable and of good quality (ISO, 2013).

1.3.7.3 The ISO standard ISO 22000:2005

Specifies the requirements for a food safety management system, the place an organization in the food chain needs to exhibit its ability to control food safety hazards, in order to ensure that food is safe at the point of human consumption and it is a management tool, used to protect the food supply chain and production procedures against microbial, chemical and physical hazards and contamination ((ISO, 2005).

ISO 22000 used to be published in September 2005. Up till this point, the HACCP system was the internationally accepted strategy for developing a food safety management system. However; HACCP did now not supply sufficient emphasis to the management of the system, hence the development of ISO 22000 which contains HACCP and ISO 9001:2000 (Uyar *et al.,* 2012).

As ISO 22000 focuses on quality and customer satisfaction as well as food safety, the adoption of this system in the food service facility of a hospital is expected to enhance the patient experience and lead to improvement in patient satisfaction levels. Furthermore, ISO 22000 leads to the retention of food quality and the nutritional value of the food thereby improving the result of the patient (Uyar *et al.,* 2012).

Only one study could be found in the literature on ISO 22000 implementation in a hospital food service facility. This study used to be performed in Turkey by means of Uyar *et al* in 2012. The objectives of this learn about have been to determine the variations in patient satisfaction before and after ISO 22000 implementation and to determine the elements affecting satisfaction levels with the hospital food and food service (Uyar *et al.,* 2012).

ISO 22000 derives an awful lot of its shape and content from HACCP, integrates all of the HACCP concepts as properly as basic good hygiene practices and prerequisite programmes for food safety, as outlined in SANS 10049:2012. While HACCP is inherently a system to prevent food safety hazards; ISO 22000 recognizes that new food safety hazards emerge and new technologies to control food safety hazards are developed.

Therefore, ISO 22000 makes use of a systems approach to prevent new dangers from happening (Surak, 2007). ISO 22000 involves the implementation of an

operational prerequisite programme which places emphasis on the essential risks recognized in the hazard analysis, in order to decrease the probability that food products will uncover or contaminated or that risks will proliferate (Arvanitoyannis and Kassaveti, 2009).

Is a HACCP kind standard especially developed to assure food safety? ISO 22000 will dynamically combine the HACCP principles and application steps with prerequisite programmes, using the hazard analysis to determine the strategy to be used to ensure hazard control by way of combining the prerequisite programmes and the HACCP plan (Faergemand and Jespersen, 2004). The new standard offers an alternative to food enterprises that they do not enforce ISO 9001 and they prefer an effective food safety management system (Aggelogiannopoulos *et al.*, 2007).

1.3.7.4 The benefits of ISO 22000:2005:

Involving quality management, external and in-house communications, designating responsibility, enforcing disaster management, continual improvement, and excellent health practices (Aggelogiannopoulos *et al*., 2007).

1.3.7.5 A present-day science-based food safety system approach is :(FAO, 2006)

(i) Preventive approach.

(ii) Addresses the farm-to-table continuum.

(iii) Use structured risk analysis and establishes priorities.

(iv) Relies on built-in process control and shared responsibility.

(v) Enables attainment of an enhanced level of risk reduction.

1.3.7.6 Challenges and shortages

The standard does not provide a guideline considering procedures due in one product may not be excellent in another. ISO 22000:2005 is no longer recognized by way of GFSI due to the lack of technical specification for area PRPs. In a combination with PAS 220, ISO 22000 is known as FSSC 22000 and is recognized by GFSI.

food quality management is problematic due to the fact it includes the complex characteristics of food and their uncooked materials due to variability, constrained shelf life and their large range of (bio) chemical, physical and microbial processes (Spiegel, 2004).

ISO 22000 is an international, auditable standard that specifies the requirements for food safety management system through incorporating all the factors of (HACCP)

together with a comprehensive management machine (Pillay and Mulayam, 2005).

1.3.7.7 ISO 9000 family of standards

The International Organization for Standardization (ISO) published the ISO 9000 series of standards in 1987. This series of standards "provide guidance and equipment for companies and organizations who want to make sure that their products and services consistently meet customer's requirements, and that quality is consistently improved" (ISO, 2014c). These standards have been developed to guide organizations of all kinds and sizes to put into effect and operate effective quality management systems (ISO, 2005). Within this series of standards, the ISO 9000 family includes 4 different standards.

1.3.7.7.1 ISO 9001:2008 (ISO, 2008b): sets out the requirements for a quality management system where an organization can reveal its functionality to supply

products and services that fulfill customer and regulatory requirements and aims to increase customer satisfaction (ISO, 2005; ISO, 2009c).

1.3.7.7.2ISO 9000:2005 (ISO, 2005): describes the fundamentals of quality management systems and explains the vocabulary used in the ISO 9000 family of standards. It pursuits to create a basic understanding of quality management described in ISO standards. Moreover, it introduces eight Quality Management Principles and the use of the process approach for continual improvement (ISO, 2005; ISO, 2009c).

1.3.7.7.3ISO 9004:2009 (ISO, 2009a): gives guidelines on effectiveness and effectivity of a quality management system. It aims to assist organizations in managing long-term success. It is recommended for groups that are inclined to prolong the benefits received from ISO 9001 and to systematically and continually improve the organization's overall performance. It is used to extend advantages received from ISO 9001 to the events that are fascinated in or affected by means of an organization's operations. These include employees, owners, suppliers, partners and society in general (ISO, 2005; ISO, 2009c).

1.3.7.7.4 ISO 19011:2011 (ISO, 2011): gives guidelines for the inside and external auditing of quality management systems and environmental management systems. It includes information on the audit programs, how to conduct an interior or external audit, and auditor competence. It presents an outline of how an audit program must operate and how audits must be carried out (ISO, 2005; ISO, 2009c).

1.3.7.8 Principles of ISO 9000

ISO 9000 sequence of standards is based totally on eight quality management principles. These principles can be used by way of organizations as a framework to enhance performance (ISO, 2012a).

1.3.7.9 ISO 9001

"needs to exhibit its ability to consistently provide a product/products that meet customer and applicable regulatory requirements," and; "aims to enhance purchaser pleasure thruough the effective application of the system, along with approaches for continual improvement of the system and the assurance of conformity to customer and applicable regulatory requirements" (International Standards Organization 2008).ISO 22000 can consequently be seen as "bridging the gap" between HACCP and ISO 9001 (Uyar *et al.*, 2012).

ISO 9001 offered a set of standards that provided a framework for quality management from manufacturing to delivery. For many firms, the ISO 9001 requirements have provided the method to meet the needs of global competition. Although obtaining ISO 9001 certification can be quite expensive, many firms still see it as a worthwhile funding that will carry sizeable returns via growing sales and reducing costs. Meanwhile, ISO 9001 has been applied by using over one million agencies in 187 countries (ISO, 2013a). Despite giant world adoption of the certification, the question remains if companies can, in reality, achieve the advantages they expect. To reply to this question, researchers have examined the effects of certification since the first companies started out implementing the standard. Unfortunately, after 25 years of research, there is nonetheless a lack of consensus about the economic influences of ISO 9001 certification.

A massive body of literature reports positive effects of ISO 9001 certification on different performance measures. For example, Naveh and Marcus (2005) discover that the use of ISO 9001 reduces satisfactory expenses and increases annual sales and profit margins. However, a few studies find evidence of the terrible consequences of certification. Given the significance of ISO 9001 amongst practitioners and its magnitude in operations management research, additional

research is critical to acquire a generalized understanding of the relationship between ISO 9001 certificate and financial performance.

There are various techniques to habits lookup into this relationship. One is a replication study. However, there is already much research about the hyperlink between ISO 9001 and monetary performance. Therefore, a replication study would only add to the pile of current conflicting conclusions. Another choice is to behave a literature review. Most of the previous literature reviews have been qualitative (Psomas and Fotopoulos, 2009, Sampaio *et al*., 2009., Rusjan and Alič, 2010). However, due to the massive wide variety of current studies and the various design, context, and measurement of these studies, qualitative integration of research findings may lead to imprecise syntheses (Hunter and Schmidt, 2004). A recent paper by way of Boiral (2012a) is the first paper that opinions the literature quantitatively, but it does no longer go beyond reporting the percentage of studies that found an advantageous effect of certification. Meta-analysis is an alternative method. It allows researchers to critically have a look at and integrate research findings across one-of-a-kind studies quantitatively. However, the use of meta-analysis is still limited, though it is growing in the management area (Gooding and Wagner, 1985; Capon *et al*., 1990; Crook *et al*., 2008; Stahl and Voigt, 2008; Wu and Lederer, 2009; Chen *et al*., 2010 and Carney *et al*., 2011).

1.3.8 Quality Management System (QMS):

The definition of the quality management system is, according to American Society for quality," a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives". Oakland (2014) defined the QMS as" an assembly of components, such as the management, responsibilities, procedures, and assets for implementing total quality management". The purpose of a quality management system is to improve

processes, decrease waste, decrease costs, facilitate and identify training purposes, engage the staff and set an organization-wide direction. A suitable QMS ensures that each customers' and organizations' requirements are met. (Oakland 2014)

Since the beginning of the QMS era the International Organization for Standardization (ISO), a non-government community of national requirements institutes, has developed numerous standards for the useful resource in an organizations pursuit to attain quality. The most regarded is perhaps the ISO 9001 standard for quality management.

Nowadays there are standards for nearly everything. A few examples are given in the ISO (2017) published ISO and food – Great things happen when the world agrees. There is, for instance, a standard, ISO 7304, which gives guidelines for cooking pasta to perfection, every other one, ISO 3103, which defines what makes a good cup of tea and sooner or later an ISO 3959, outlining the high-quality prerequisites for ripening inexperienced bananas.

In addition to the above there are additionally several, possibly more usable, Microbiology requirements to help determine what the secure ranges of micro-organisms are, e.g. ISO 16140 Microbiology of the food chain – Method validation and ISO 6579-1 which explains the process for detection of salmonella. These are only a fraction of the range of standards related to food (ISO, 2017).

Table: 1 ISO 22000 family (Granholm, 2017)

Table 1. ISO 22000 family (ISO n.d.).

ISO 22000 family	
Standard	**Title**
ISO 22000:2005*	Food safety management systems -- Requirements for any organization in the food chain
ISO/TS 22002-1:2009	Prerequisite programmes on food safety -- Part 1: Food manufacturing
ISO/TS 22002-2:2013	Prerequisite programmes on food safety -- Part 2: Catering
ISO/TS 22002-3:2011	Prerequisite programmes on food safety -- Part 3: Farming
ISO/TS 22002-4:2013	Prerequisite programmes on food safety -- Part 4: Food packaging manufacturing
ISO/NP TS 22002-5**	Prerequisite programmes on food safety -- Part 5: Transport and storage
ISO/TS 22002-6:2016	Prerequisite programmes on food safety -- Part 6: Feed and animal food production
ISO/TS 22003:2013***	Food safety management systems -- Requirements for bodies providing audit and certification of food safety management systems
ISO 22004:2014	Food safety management systems -- Guidance on the application of ISO 22000
ISO 22005:2007	Traceability in the feed and food chain -- General principles and basic requirements for system design and implementation
ISO 22006:2009	Quality management systems -- Guidelines for the application of ISO 9001:2008 to crop production

* Will be replaced by ISO/DIS 22000
** Currently under development
*** Will be replaced by ISO/DIS 22003

1.3.9 IFS

In a statement done by IFS (International Featured Standards, 2010) one can read: "Standards of product and manner quality are an inevitable part of today 's food-production landscape. In the global marketplace with international flows of goods, a validated standard has emerged as indispensable." The quality and food safety standard IFS Food used to be created in 2002 for the private labels of retailers and is today in use both for private and industrial label retail brands. In a pamphlet from IFS (2010) the country that their mission is to develop an umbrella brand for product safety. IFS has developed standards no longer only for food protection but for logistics, household and personal care products, brokers and wholesale business, the current version of IFS Food is the fifth version. After the audit

introducing IFS Food in a food production site, IFS permit a length of 12 months for corrective actions. This is to provide the company enough time to work on and increase their approaches in accordance with the standard. Worldwide, 12,000 suppliers are licensed in accordance with IFS Food (IFS, 2010).

1.3.10 FSSC 22000

FSSC 22000 is a countrywide control system developed by the Foundation of food safety certification, with the support from Food and drink industries of the European Union (CIAA) (Veritas, 2007). The standard is based on ISO 22000 and PAS 220 where the purpose of the first is to provide a tool for the management to control and minimize food safety hazards and to make sure compliance. PAS 220 was once developed to specify requirements on prerequisite applications (PRP) to manipulate food safety hazards all through the food processing and to guide management systems applied to fulfill the ISO version. FSSC 22000 has received worldwide awareness seeing that situated in 2004 and the general is relevant to all sorts of organizations in the food chain (FSSC 22000, 2). It applies to producers and producers of perishable vegetal products, products of animal origin, long shelf-life products, food packaging manufacturing and food ingredients such as additives, bio-cultures, and vitamins, regardless of complexity or size of the organization, public or privately owned or if it is profit-making or not.

Certification bodies that are licensed to difficulty approved FSSC 22000 certificates are these those have an agreement with the FSSC basis (ibid.), the standard is governed by means of a board of stakeholders involving representatives from all parties.

FSSC (The Foundation for Food Safety Certification) is a Dutch maintained and GFSI approved certification program, which is based on the ISO 22000 standard.

In contrary to ISO 22000 the FSSC 22000 is utilized on the complete food chain and the organization must, in addition to the ISO 22000 requirements, additionally comply with the region-specific PRP-program necessities of ISO/TS 22002-1 and the extra requirements in the FSSC 22000 Scheme (Additional requirements for the food security system, Part II). The additional requirements in FSSC 22000 aim to make sure consistency and integrity as properly as supply governance and management of the Scheme (Lassheikki *et al.*, 2016). The first version of the FSSC 22000 was once published in 2010. In 2016 version four was launched internationally and is stated to be more transparent and easier to understand than previous versions. The trendy version, 4.1, was once drafted only a few months after version 4, because of developments influencing the FSSC 22000. Starting from 1st of January 2018 all audits will be according to version 4.1.(Veritas ,2017).

1.3.11Challenges:

A lot of the facts concerning requirements and certificates come from the certification organizations themselves or from accreditation firms. Therefore, the statistics are often one-sided positive, but there are some negative aspects regarding certificates too. One of them is the phenomenon of ’soft grading’, which means that when a company is required to put in force a standard due to a requirement from a consumer they might pick out the most convenient way to earn the certificates (Hellqvist, 2012). This undermines the credibility of the widespread and paves the way for less serious certification organs Standards can be obstacles to exchange however they can additionally be catalysts to alternate (Lusk *et al.*, 2011). Depending on a variety of factors there is a threat to both ‘under’ or ‘over-standardization’ when a food producer implements a standard in their production. This is one of the reasons for the current want for controls made by using a 1/3 celebration who monitors and accredits standards implemented in food

manufacturing (Stigzelius, 2009). Many retail companies require that their supplier implement a standard in the production. In a study of dairy producers by Eriksson (2009), this is considered as a negative improvement due to the double charges and the double reviews. Many of the dairy producers in the study consider the supervision executed through certification bodies and municipal controller's very similar. DNV (2009) is of the same opinion of that food producers may additionally have to undergo various audits based totally on different standards considering the fact that there are no accepted popular for food safety audits.

1.3.12 According to Mensah and Julien, (2011) the advantages of FSMS compliance are:

1. Increased purchaser satisfaction.

2. Improved interior procedures.

3. Improved product quality.

4. Compliance with regulatory requirements.

5. Improved corporate image.

6. Improved employee morale.

7. The enhanced prospect of buying and selling in different countries.

8. Reduced running costs.

9. Lower insurance charges.

1.3.13 Mensah and Julien, (2011) note that the motivations for FSMS compliance are:

1. Product quality improvements.

2. Customer requirements.

3. Regulatory requirements.

4. Enhanced marketing advantage.

1.3.14 Challenges of FSMS implementation

FSMS implementation faces a variety of challenges when being applied and maintained. These challenges normally manifest at the implementation stage of the FSMS but are not constrained to it. Mensah and Julien, (2011) noted that the challenges of FSMS compliance are:

1. Employee resistance to change.

2. Lack of technical know-how and talent of employees.

3. Lack of recognition of the requirements.

4. The excessive fee of improvement and implementation.

5. Inappropriate infrastructural abilities for validating and verifying an FSMS.

6. The excessive cost of education and training.

7. Blame culture.

8. Rapid changes in regulation.

9. Lack of getting admission to ample information.

10. Lack of authorities' support.

1.4 **HACCP:**

In an evaluation of worldwide methods to the use of HACCP. Ropkins and Beck (2000) mentioned that HACCP principles have been incorporated into the food safety legislation of the USA, Canada, Australia, New Zealand, The Netherlands,

Germany, and the UK. Since the January 2006, the European Parliament has made it obligatory that all food commercial enterprise operators of member states establish and enforce food safety programmes based on the HACCP standards (Domenech *et al.*, 2008). In creating countries, HACCP has been tough to put in force due to a number of obstacles and issues such as education and training, language difficulties and availability of nearby food safety hazard records (Ropkins and Beck ,2000).

1.4.1 **Benefits of HACCP implementation**

This ADA (American Dietetic Association) record via Gerald and Perkin (2003) highlights the increased implementation of HACCP as one of the motives that bacterial foodborne illnesses have been drastically decreased in the United States of America (USA) in the duration 1996 – 2003.

Hanekom *et al.* (2010) carried out a study in a food service unit of a private health facility in Gauteng, South Africa to check out the hygiene and food safety status of the unit serving low microbial diets to immune-compromised patients. The investigation was once accomplished using an audit shape primarily based on HACCP principles in one of a kind area of the unit. Four random food samples and four random floor swabs were taken and sent for microbiological analysis. The outcomes of the audit and microbiological testing had been used to consider feasible food safety risks in the unit according to internationally approved HACCP standards. The results of the study revealed several food safety contraventions as well as high microbial counts on numerous of the samples and swabs. This highlighted the truth that even though food safety tactics had been reported to be in place in the unit, they have been no longer followed.

Hanekom *et al.* (2010) concluded that the HACCP system is an ideal, proactive method to make certain food safety in a health center food service unit and is vital to produce hygienically safe food. This supports the research performed by way of Lund and O'Brien (2009) who pronounced that most foodborne outbreaks in health care services should have been averted through suitable hygiene practices and HACCP.

Recommendations for prevention of foodborne nosocomial infections given with the aid of Greig and Lee (2012) consisted of education of the food handlers, monitoring of food temperatures, more precautions for vulnerable patients and effective hand washing, all of which form part of the pre-requisites for a HACCP system.

1.4.2 **Benefits of the HACCP system**

In hospital food service has been reported in more recent research performed in Iran, Turkey, Spain, Taiwan, Greece and the UK. The benefits stated included extended affected person satisfaction, a decrease in grievance rates, prevention of food poisoning episodes, the avoidance of unnecessary costs and elevated consumer confidence (Griffiths 2006; Gikas *et al*, 2007; Rodriguez, *et al* 2011; Shih and Wang 2011; Uyar *et al*, 2012 and Farzianpour *et al*, 2014).

1.4.3 **Barriers to HACCP implementation**

Shih and Wang (2011) investigated the limitations that can also affect HACCP implementation in Taiwanese public hospital kitchens. Catering managers in 23 hospitals participated in the study, through completing a questionnaire concerning the difficulties and advantages of HACCP implementation. It was once observed that many food service staff do now not understand the system and therefore have a concern of implementation, highlighting the want for intensive training for all

levels of food service group of workers on the HACCP principles and its benefits. Other possible factors affecting HACCP implementation as reported by Shih and Wang (2011) had been the provision of adequate funding as properly as gender, age and job position of food carrier staff. The female group of workers has been more tremendous about HACCP implementation compared to the male group of workers and it was suggested that this can also be due to the fact women pay extra attention to specific cleansing and hygiene than males. The older team of worker's contributors and those in lower job positions experienced decrease levels of job satisfaction compared to younger, extra senior employees and this negatively impacted on their motivation to be involved in the HACCP implementation technique (Shih and Wang, 2011). Similar findings have been mentioned by using Baracoa *et al.* (2011) who investigated advantageous HACCP implementation in particular within contract catering companies in Spain and said lack of group of workers coaching and motivation as well as lack of financial and economic sources as difficulties to the effective implementation of HACCP systems (Garayoa, *et al,* 2011).

The study through Shih and Wang (2011) also observed that amongst foodservice management, the degree of difficulty of HACCP implementation was lower than expected. Managers firstly had little self-belief in receiving support, funds, and resources from the hospital management, alternatively, it was located that support and education had been supplied which had assisted in the implementation procedure.

Managerial attitudes in the direction of the HACCP system was investigated in Hungary by Banati and Lakner (2012) and it was once observed that 41% of food service managers had a reluctant mindset towards HACCP, due to fear of increased administrative burden and added costs. These consequences highlighted the

significance of a built-in approach to HACCP in managerial obligations in an effort to well known the benefits of HACCP for a higher organization of the facility (Banati and Lakner, (2012).

The need for basic food protection and food hygiene training for food provider staff is of imperative importance, before the implementation of any food safety management system, which includes HACCP. Although many food service workforces might also recognize the importance of food security in a hospital environment, their attitudes and food hygiene practices are often lacking. This used to be a common finding in research performed in Turkey, Italy, Spain and Greece (Angelillo *et al.*, 2001; Ayçiçek, *et al.*, 2004; Gikas *et al.*, 2007; Tokuç, *et al.*, 2009 and Rodriguez, *et al.*, 2011).

1.4.4 **Hazards analysis critical control points (HACCP)**

HACCP system is a food safety management strategy which has been widely tested and established as an effective capability of stopping food-borne diseases have been effectively implemented (WHO, 1993). It is considered a scientific and systematic system for assuring food safety (Nguyen *et al*., 2004), which can be applied at some point of the complete food chain (Domenech *et al*., 2008).

Hazards analysis critical control points (HACCP) used to be developed as a management tool to provide an extra structured strategy to manage identified hazards. PR/HACCP is a continuous, comprehensive food, protection monitoring system designed to prevent hazards from developing along the manufacturing process, for that reason making sure a high diploma of food safety (Bjerklie, 1992; Karr, *et al*., 1994). It units up a framework allowing the distinctive examination of a technique to discover hazards and the place the risks can be managed (Khandke and Mayes, 1998).

1.4.4.1 **USES**

Literature showed that HACCP has been in the location in hospital foodservice departments on account that at least 1993 (Richards *et al.,* 1993). It has been reported that this simple and logical system makes it a perfect tool for both medical institution contamination control and food hygiene practices and therefore the health departments of many international locations have prompted the implementation of HACCP in hospitals (Barrie 1996; Osborn, *et al.,* 1997; Angelillo, *et al.,* 2001; Gikas, *et al.,* 2007; Kokkinakis *et al.,* 2011; Shih and Wang 2011). Several researchers have tested the price of HACCP in hospitals, which include the identification of possible hazards before they occur, the high degree of involvement of all catering staff, improved food safety practices and the potential of the system to elevate each the excellent and security of the food that is produced (Richards *et al.,* 1993; Barrie 1996; Angelillo *et al.,* 2001; Gikas *et al.,* 2007; Kokkinakis *et al.,* 2011 ; Shih and Wang 2011). Other studies have proven an enhancement in food safety audit results and the microbiological results of surface, equipment and hand swabs as well as food samples taken from hospital kitchens the place HACCP has been implemented (Shanaghy, *et al.*, 1993; Oliveira, *et al.*, 2001; Farzianpour, *et al.,* 2014). In a hospital setting, a HACCP-based system is endorsed to prevent, eliminate or minimize the probability of serving contaminated food to an affected person (Stamey, 2006).

1.4.4.2 **HISTORY:**

HACCP is a management tool developed in the late 1960s, to make sure the protection of foods for area travels (Ropkins and Beck, 2000). HACCP system is designed to be used to stop the occurrence of food-borne risks from production via manufacturing, storage, and distribution of a food product (Surak, 2003). It, used to

be first added as a joint challenge between NASA and the Pillsbury Corporation in the early 1960s (Mayes and Mortimore, 2001).

HACCP was at the start created to eliminate the microbiological hazards from outer space but also increase the confidence that the space program could successfully hold personnel safety. The predominant groundwork for putting off the microbiological risks was to make certain that astronauts would be safe from ailment seeing that they would be without clinical care for several weeks (UNI DO, 2000).

Another important improvement for the HACCP program used to be the institution of the Codex Alimentarius second version in 1997. The Codex Alimentarius, which in Latin potential food law or code, used to be installed by means of the joint Food Agriculture Organization (FAO)/WHO Committee. This preferred on food hygiene was once hooked up to guard the health of customers and to make certain truthful practices in the food change (FAO/WHO, 1999).

The basis of the 2nd version was once to set up the concepts and suggestions for conducting microbiological threat assessments. The code recommends that organizations use a HACCP based approach wherever viable to decorate food safety (FAO/WHO, 1999). HACCP has evolved over the years due to the advances in the quality management field, which in flip has allowed food processors to enhance a food safety management system (Surak, 2006).

Today, with the help of the Food Safety Modernization Act, the FDA, and the US Department of Agriculture requires mandatory food safety programs in all food and feed manufacturing facilities (Keener, 1999). According to the FDA the new FSMA Act “will have a legislative mandate to require comprehensive, science-based totally preventative controls across the food supply” (FDA, 1999).

- **HACCP Six principles:**

Corlett (1998) emphasized that HACCP is a scientifically based protocol that is utilized directly in the food procurement, manufacturing and distribution process.

Unnevehr and Jensen (1998) describe the six ideas in growing and working a HACCP program:

1. Assess the hazard, listing the steps in the manner where sizable risks can occur and describe the prevention measures.

2. Determine quintessential control CCP in the process.

3. Establish indispensable limits for each CCP.

4. Establish corrective movements to be taken when monitoring indicates a deviation from the CCP limits.

5. Establish a report maintaining for the HACCP system.

6. Establish methods to confirm that the HACCP system is working correctly.

But (Wellington, 1997), makes it seven principles.

1.4.4.4 The HACCP system consists of the following seven principles:

- **Principle 1:** Conduct a hazard analysis.
- **Principle 2:** Determine the critical control points (CCPs).
- **Principle 3:** Establish critical limits
- **Principle 4:** Establish a system to screen control of the CCP.
- **Principle 5:** Establish the corrective action to be taken when monitoring indicates that a precise CCP is not underneath control.

- **Principle 6:** Establish tactics for verification to affirm that the HACCP system is working effectively.
- **Principle 7:** Establish documentation regarding all strategies and files suitable to these concepts and their application.

1.4.4.5 Hazards (physical, chemical, microbiological)

The rules defines a meals protection hazard as 'Any biological, chemical or physical property that can also reason the food to be risky for human consumption' (USDA,1997).

1.4.4.5.1 Physical hazards

Physical hazards consist of glass, metal, stones, wood, plastic, rubber or pests (typically larger pests). Sand may additionally also be an undesirable overseas material in a prepared salad however it is now not in all likelihood to reason human sickness (Harris,1999).

1.4.4.5.2Chemical hazards:

Chemical risks consist of cleaning chemicals, pesticides (including those now not utilized in or around food processing establishments), allergens, poisonous metals, nitrites and nitrates (when brought to the product), plasticizers and packaging migration, veterinary residues (when animals have been given drugs to deal with disorder in the animal, e.g. antibiotics treatments for mastitis in cows and chemical additives (when added) (Harris, 1999). Between 5 and 8% of children and 1– 2% of adults are allergic to positive chemical substances in ingredients and food ingredients. These chemicals are commonly referred to as food allergens (McSwane *et al*., 2000).

1.4.4.5.3 Biological hazards

Biological hazards include food poisoning bacteria such as *Salmonella*, *E. coli* and *Bacillus cereus*, which are hazardous due to the fact they can live on insufficient cooking, develop to harmful degrees in stored food given the right prerequisites and unfold from uncooked ingredients to 'ready to eat foods' (cross-contamination).

1.4.4.6 Risk **analysis and modern food safety systems:**

Science-based approaches are an important and crucial part of Risk Analysis to improve food safety systems. Risk analysis presents a means to improve the ability of traditional food safety systems to meet current challenges. It offers a framework to efficaciously manage, verify and speak risks in cooperation with the numerous stakeholders involved.

In summary, the use of a science-based approach will allow governments to increase and put in force a range of general enhancements and interventions tailor-made to specific high-risk areas, which will eventually improve food safety and decrease the burden of food-borne disease. (FAO. 2005).

1.4.4.6.1 **Risk assessment: (FAO.,2005)**

It has been defined as "the process, distinct from chance assessment, of weighing policy alternatives, in session with all involved parties, considering hazard evaluation and other factors applicable for the health protection of consumers and for the promotion of truthful exchange practices, and, if needed, deciding on suitable prevention and manage options" (Codex). Risk management, therefore, performs a key role at the beginning of the risk analysis process in figuring out food safety troubles and thinking about the high-quality approaches to control them. The complete evaluation of all the on-hand management selections that

results from this procedure will assist to make certain that decision-makers are capable to make a knowledgeable choice on the most appropriate prevention and management option. Depending on the nature of the hazard and circumstances in which it occurs, a number of scientific specialists (including biologists, chemists, medical experts, geneticists, epidemiologists, toxicologists, microbiologists, agronomists, botanists, entomologists, zoologists, and others) can also be involved.

The genuine mixture of analytical equipment and methods used in qualitative and quantitative risk assessment will differ according to the unique context and kind of the danger assessment. To practice these methods and perform the chance assessment, positive primary infrastructure (including laboratories, scientific equipment, technology, and research facilities) will be essential.

1.4.4.6.2 **Risk management: (FAO, 2005)**

Risk management is an iterative process. Therefore, any model for risk management must be flexible enough to enable the various activities to be reviewed, repeated and adapted as necessary. The steps in the danger management procedure will no longer always occur in the equal order. What is most essential is that appropriate interest is paid to all the activities.

1.4.4.6.3 **Risk communication: (FAO, 2005)**

Risk communication is defined as the trade of facts and opinions regarding risk and risk-related factors among danger assessors, chance managers, consumers and other interested parties (FAO/WHO, 1998). Risk communication is a vital part of the risk analysis paradigm. The main goal of food safety risk communication is to increase understanding among various food safety stakeholders involving the reason behind the selections taken to check hazards and control food safety risks,

and to help human beings to make more knowledgeable judgments about the food security hazards and risks they face in their lives (EFSA, 2012).

Risk communication used to be viewed primarily as the dissemination of information to the public about health dangers and events, such as outbreaks of disease and directions on how to alternate behavior to mitigate these risks. Thinking on this has now advanced dramatically as social science proof and new communication and media technologies and practices have evolved in the 21st century. The three huge shifts (Gamhewage, 2013) that have influenced the field for risk communications are:

1. Experts and authorities are much less trusted, and a problem of real or perceived have confidence is now central to health communications and risk communications.

2. The way the public is searching for health advice has shifted to the public online sources, and social networks.

3. The way the media works has modified to include 24-hour journalism; the discount in resources and "beat experts" to observe health news; the increase of citizen journalism and social media, and the rise of opinion versus the properly sourced and referenced new stories of the past.

1.4.4.7 **Residues history**

Health is related to without delay to the environment (EPA, 2015), and in particular the nature and high-quality of the food (Ames, 1983). Quality of food from animal products is broadly concerning public health agencies around the world given that veterinary drugs have performed an essential role in the field of animal husbandry

and agro-industry, and increasing prevalence of residues, and resistance have become interesting issues (Rokka *et al*. ,2005).

Veterinary drugs or veterinary medicinal products (VMPs) are critically needed to meet the challenges of providing enough quantities of food for the developing world population (Crawford,1985) as drugs improve the rate of weight gain, enhance feed efficiency, or prevent and treat diseases in food-producing animals (Crawford, 1985 and AVMA,2015).

Antibacterial drugs and hormonal growth promoters are the main VMPs that potentially contaminate foods of animal origin (Takele *et al*., 2015). Hence, veterinary two drugs or VMPs residue is one of many world troubles regarding food contamination (Ames,1983 and Rokka *et al*., 2005). Residues, as defined by means of the European Union (EU) and the Center for Veterinary Medicine, an organization below the Food and Drug Administration (FDA/CVM) in the USA are "pharmacologically energetic substances (whether lively principles, recipients or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the VMPs in query has been administered" (EC,2010). Under the regular physiological conditions, following administration of a drug to an animal, most drugs are metabolized in order to facilitate elimination, and to a giant extent cleansing as well. In general, most of the parent product and its metabolites are excreted in urine and a lesser extent with the aid of feces (Boothe and Reevers., 2012). However, these substances may additionally be determined in milk and eggs, and in the meat (VICH, 2011).

1.4.4.8 **Types of Residues**

1. 4.4.8**.1 Pesticides**

More than one hundred pesticides are known; however, it is unlikely to discover all of them in one foodstuff.

They are usually used in agriculture (68%), commercial and industrial activities (17%), and domestic settings (8%) and in governmental applications (7%) (Cantoni and Comi, 1997). A massive quantity of pesticides can also potentially be used in the production of agricultural crop commodities, leading to indirect exposure of animals thru feed and the achievable for residues in animal products (MacLachlan and Bhula, 2008).

Animals can also be uncovered to pesticides by using ingestion of contaminated soil while grazing. Less frequent sources of farm animal's exposure to pesticides include unintended spills, wrong waste disposal and contaminated areas from past use of products that are continual in the environment (Robertson and Joyce., 1990), and may additionally be incompletely eliminated at the time of slaughter (Abou-Arab, 2002 and MacLachlan and Bhula, 2008).

Pesticides may additionally set off positive health troubles in humans such as cancer, immune device disturbances and disruption of hormonal functions (Vincenzo *et al*., 2002). Although DDT had been banned, however, a widely used insecticide persists in animal tissues. Other cyclodiene groups additionally tend to accumulate in body fats (Ruiter, 1985).

The accumulation of pesticides in the liver may additionally be as a lot as 100 times higher than other physique tissues (Ruiter, 1985). Consumer opinion surveys point out that a lot of the U.S. public believes that pesticide residues in food are most serious cancers hazard (ORC, 1990).

There is, alternatively lack of public understanding of the substantial evidence indicating that excessive consumption of the foods that contain pesticide residues

(fruits and vegetables) has a protective effect against many types of cancer. A overview of about 200 epidemiological research reported a steady affiliation between low consumption of fruits and vegetables and most cancers incidence at many target websites (Ames *et al.*,1990b; Steinmetz and Potter, 1991; Block *et al*., 1992; Hill *et al*., 1994) estimated that each day average U.S. publicity to natural pesticides in the diet is about 1500 mg and too burnt material from cooking is about 2000 mg.

1. 4.6**.2 Heavy metals**

Anthropogenic activities may also have an adverse impact on human health due to the discharge of industrial waste and home sewage (GRC, 2006). These effluents usually incorporate accelerated levels of heavy metals that accumulate in macro-particles, which form the groundwork of many food chains (Alloway and Ayres, 1997). Lead interferes with hemoglobin synthesis and is able to inhibit numerous enzymes (Ruiter, 1985). Cadmium accumulates in the kidneys and it has an extraordinarily lengthy biological half-life in humans in the order of 20-30 years (WHO, 2009). Cadmium concentrations in old animal tissues are occasionally extremely high. Mercury tiers above 0.05 mg/kg in meat and fish merchandise should be regarded as harmful or hazardous. Copper and thallium are also elements that warrant problem (Ruiter, 1985).

1. 4.6**.3 Melamine**

Melamine (2,4,6- triamino -1,3,5-triazine) is an organic compound commonly used to produce various products, such as dishes, plastic resins, in fertilizer, as a flame retardant, manufacture of wrinkle-free textiles and components of paper and paperboard that may meet meat (Garber, 2008). It can also be present indirectly in foods of animal origin as a result of carryover from the intentional addition to

animal feed, therefore, there is an urgent want to detect melamine in foods (Sivaraman, 2007 and Varelis, 2008).

1.4.6**.4 Genetically modified products Plant** food produced thru genetic engineering, in a purpose to produce desirable traits, have reached the consumer markets. After 12 years of commercialization of biotech crops, the international place of planted biotech vegetation has multiplied extra than 80-fold, from 1.7 million hectares in 6 international locations in 1996 to 143 million hectares in 23 international locations in 2007 (Magana and Calderon, 2008). The most cultivated genetically modified plant is the soybean, which represents the staple constituent of many processed meat and fish products. Soybean meal is also the major source of protein in livestock diets and its used widely in meat and fish products. Because it has a unique way to emulsify the products due to the functional properties such as water binding, fat binding, texture, and emulsifying capability and organoleptic features such as appearance, firmness and slicing characteristics (Belloque *et al*., 2002).

1. 4.6**.5 Mycotoxins**

One of the most dangerous pollutions of food is fungi and their metabolites – which can cause mycotoxicosis. They are typically from the species *Aspergillus*, *Fusarium* and *Penicillium*, aflatoxins, ochratoxins, zearalenone, trichothecenes, and fumonisins (Maria and Mary 2012). Mycotoxins are found on many plant products, specifically oilseeds, and cereals. These supplies are characterized by using acute and chronic poisonous properties, while some of them are highest potent cancer-causing agents same as aflatoxins B1. Although animals are an effective toxin eliminator (Stoloff, 1979), however, the residues of mycotoxin can still be present in animal tissue because they are stable and heat resistant compounds (Kadim, 2014).

1. 4.6.**6Anabolic compounds**

Anabolic agents influence the metabolic functions of animals resulting in an increased growth rate and an expanded deposition of proteins in the muscle mass via decreasing the fat content in the carcass and increasing meat leanness (Lone, 1997).

The residues of anabolic agents or their metabolites in fish, meat and different foods of animal origin may cause adverse toxic effects on consumers' health. Serikbayeva, A. and A. Ospanova reported in 2016, the presence of anabolic residues in animal feed (meat and meat products), can also cause risks to the consumer and It has been shown that there an association between some forms of hormone-dependent cancers and red meat consumption (EFSA, 2007). Barbosa *et al*.(2005) said the consumption of lamb and bovine meat containing residues of Clenbuterol resulted in 50 intoxicated peoples with signs and symptoms described as gross tremors of the extremities, tachycardia, nausea headaches, and dizziness.

1. 4.6.**7Parasitic Drugs:**

Parasitic helminths infection impacts food-producing animals worldwide. Example; Ivermectin is a broad-spectrum macrocyclic lactone endectocide and is widely used for the treatment and prevention of both nematode and arthropod parasites in food-producing animals. Ivermectin has been shown to be effective in the treatment of *Ascardia columbae* and *Capillaria spp*. in pigeons (Schepkins *et al*., 1985). Ivermectin is lipophilic and residues will be found in the tissues of the treated animal, particularly in those with a high fats content. The meat withdrawal time of ivermectin in mammalian livestock is lengthy (Baynes *et al*., 2000).

1. 4.6.**8Antibiotics**

One such practice that has attracted the public's attention is the use of veterinary drugs in agricultural settings and their potential presence as residues in food products (Bruhn, 1999; NRC, 1999; Resurreccion and Galvez, 1999; Willis, 2000; and Verbeke *et al*., 2007). Results from a survey conducted in the U.S. with the aid of Nicholls and co-workers (1994) indicated that many consumers erroneously believe that exposure to chemicals in foods is one of the leading reasons for death. Similarly, in the fall of 2005, the Eurobarometer survey showed that European consumers rank presence of chemicals, pesticides and poisonous substances in food second after food poisoning as their main food-related concerns (Becker, 2000; EC, 2006).

1.4.6.9 **Residue Avoidance:**

1.4.6.9.1 Monitoring of Residues in Food products

Similarly, the report of the FDA-Residue Monitoring Program for the fiscal years 2004-2006 included over 7,000 samples collected from food products such as grains and grain products, milk and dairy products, eggs, fish, shellfish and different aquatic products, fruits, vegetables, nuts and edible seeds, water, snack foods, as properly as the feed used as food for production animals. All of these exams are conducted in the raw ingredients and as part of the Total Diet Study (FDA-TDS, 2008, 2009).

It is vital to consider that in most cases the complexity of the food matrices and the different physicochemical characteristics of each possible contaminant make it difficult for the development of analytical methods appropriate for a great variety

of contaminant/food type combinations (Marazuela and Bogialli, 2009). Accordingly, analytical methods want to be developed or modified for the specific kind of contaminant and food matrix to be analyzed. Additionally, to improve validation of analytical techniques for most contaminants in foodstuffs there is a need for the development of certified reference materials and matrix blank materials for every one of the different types of food matrices (Zeleny *et al.*, 2006).

1.4.4.9.2 Pharmacological principles

To implement an effective residue avoidance programs in a food animal practice, a veterinarian must be aware of pharmacological principles of many drugs. Half-life

it means the time it takes to remove 50% of the drug from the animal and used to estimate withdrawal time. A drug with a large volume of distribution (Vd) generally has relatively good tissue distribution compared with drug of restricted distribution. The utility of viewing half-life as a function of the Vd and clearance (CL) is that these independent parameters reflect the underlying physiology of the animal. Finally, another determinant of the elimination halftimes for slowly absorbed drugs administered extravascularly is the charge of absorption. If this process is lower than elimination half-life, functionally becomes the biological halftime. With depot and sustained release preparations, this phenomenon takes on elevated significance to residue avoidance (IDF,1995). The problem facing veterinarians is that most pharmacokinetic parameters have been determined in healthy animals. Yet diseased animals would be expected to alter physiology. The sickness may additionally also prolong absorption half-lives (decreased blood perfusions of muscles, altered gastrointestinal transit times, etc.) to the point that the elimination profile is distinctive from normal animals. Based on this simplified overview of primary pharmacokinetic principles, the relationship of the half-life of

the withdrawal time can use to reduce the incidence of violative residues. Doubling dose of the drug only prolong the approved withdrawal times by way of one half-life; however, doubling the half-life because of the disease would double the necessary withdrawal time pathophysiologic states that increased Vd and/or CL would be predicted to prolong half-life (IDF,1995).

1.4.4.9. 3 Control and preventive

According to AVMA and NMPF, (1991) and Scippo *et al*, (1994), the residue control strategy is based on a -step approach:

(1) The detection of residues the use of sensitive tests with a low charge of false negatives.

(2) Followed by confirmation, requiring quantification against the MRL and identification with a low fee of false positives (Mensah *et al*., 2014).

1.4.4.9. 4 The residue prevention strategy

It is is based on preventing entry of violative residues in meat or milk intended for human consumption by means of proper drug use guide developed for use via both veterinarians and food animal (dairy and beef) producers include the following:

1- Herd health management:

All food animals must be maintained in a clean and healthful environment whenever possible.

2- Drug residues are best avoided by:

A-implementing management practice (good nutritional to meet growth, maintenance, and lactation needs)

B- herd health program that preserves animals healthy and producing efficiently; Use of authorized drugs; dairy and beef producers not use or save un-approved drugs, special mixes, or products within adequate labels as unapproved drugs have no data regarding efficacy, safety, or withholding time.

3-Establishment of valid veterinarian-client-patient relationships; the use of prescription drug and the two ELU necessitate a veterinary-client-patient relationship, which is established hence a veterinarian is close with the owner in health management of the herd.

4-Proper drugs administration and identification of treated animals; before administering or dispensing drugs one must know the drugs approved for all classes of cattle on the farm and be familiar with approved dosage, route of administration, and withholding time.

5-Proper maintenance of treatment records and identification of treated animals; institute a workable health record for every animal to file all health-related events, including administration of medication.

6-Record the identification of all animals in the permanent health record book.

7-Having proper drug residue testing capabilities really available on the farm; this control point addresses the conditions under which residue testing should be considered.

8-The proper selection and interpretation of tests; the inherent limitation and potential misuse of residue testing.

9-Creating awareness of proper drug use, and methods to avoid marketing adulterated products principally educational, total residue avoidance program is

based upon the objective of improving the livestock producer's management and quality control of marketing animals with emphasis on avoidance of drug residues.

1.5 **The Antibiotic**

The term antibiotic used to be coined from the phrase „antibiosis" which means „against life". In the past, antibiotics had been organic compounds produced with the aid of one microorganism which is toxic to different microorganisms (Russell, 2004). As result of this notion, an antibiotic was originally, largely defined as a substance, produced by one microorganism (Denier *et al*., 2004), or of biological origin (Schlegel, 2003) which at low concentrations can inhibit the increase of, or are lethal to other microorganisms (Russell, 2004).

Antibacterial is described as compounds that are capable, at low concentrations, of killing or inhibiting the growth of microorganisms (Botsoglou and Fletouris, 2001; Walsh, 2003). The term antibacterial includes two general instructions of these drugs: antibiotics which are of natural origin and antibacterials which are synthetic or semisynthetic compounds (Hagren *et al*., 2005; Marazuela and Boglialli, 2009). Both types of antibacterial drugs are used for the control, prevention, and treatment of diseases in animals are similar to those used to treat human beings (Crosby, 1991 and Prescott, 2008). Antibacterials have been used in agriculture since the 1940s to improve animal well-being and production (Jones and Ricke, 2003). Currently, there are over 7,000 identified antibacterials and several hundred specific antibacterial applications are approved for use in the U.S. for animal production. In the U.S. the Animal Health Institute estimated that annually over 8,000 metric tons of these compounds are used in the production of the three-major food-producing animal species (swine, cattle, and poultry), whereas the Union of Concerned Scientists estimated that quantity at over 11,000 metric tons per year (Mellon *et al*., 2001). In different parts of the world the use of antibacterials

remains relatively unregulated and undocumented, therefore comprehensive reports on the quantity and kind of antibacterials used for agricultural purposes in the world are unavailable (Katz and Ward, 2004).

Studies are also conducted to evaluate the patterns of absorption, distribution, biotransformation and excretion of the drug, as well as the amounts, persistence, and nature (parent drug and/or metabolites) of any drug derived residue in the edible tissues of the treated animal (Riviere, 1991; Martín-Jiménez and Riviere, 1998). The results of these studies and these from the total residue depletion study and metabolism studies are used to identify possible reservoir websites and determine the time required for the depletion of all drug-related residues from the animal and its suitable for eating tissues (Clement, 1995; CVM, 2006; 21CFR500.86, 2010).

Since the late 1960s, the USDA-FSIS has administered the National Residue Program to acquire data on chemical residues in domestic and imported meat, chicken and egg products. This program is designed to provide:

1) A structured manner for identifying and evaluating compounds of concern by means of production category (including approved and unapproved compounds).

2) Capability to analyze for compounds of concern.

3) Appropriate regulatory follow-up of reports of violative tissue residues.

4) The collection, statistical analysis, and reporting of the results of these things to do (FSIS-NRP, 2008).

Monitoring procedures are designed to become aware of and prevent probably harmful concentrations of residues entering the food supply. The federal agencies primarily responsible for monitoring veterinary drug residue in foods are the FDA

and USDA. These sister agencies cooperate to monitor and detect violative residues (concentrations of residues that exceed the imposed tolerance levels) or illegal residues (residues of drugs Specifically prohibited from animal use (Craigmill and Cortright, 2002; Fajt, 2003).

1.5.1 **Uses:**

Antibacterial drugs are typically used in animals for therapeutic, preventative and nutritive purposes (McEwen and Fedorka-Cray, 2002).

1.5.2 **Structure and classification:**

There are several approaches to classifying antibiotics, but the most common classification schemes are based totally on their molecular structures, mode of action and spectrum of activity (Calderon and Sabundayo, 2007). Each classification is characterized via a typical core structure and the various members of the class are differentiated by way of the addition or removal of secondary chemical structures from the core structure (Guardabassi and Dalsgaard, 2004).

1.5.3 **Mode of action:** (Madigan and Martinko, 2006; Talaro and Chess, 2008; Wright, 2010)

- Inhibition of cell wall synthesis
- Breakdown of cell membrane structure or function
- Inhibition of the structure and function of nucleic acids
- Inhibition of protein synthesis
- Blockage of key metabolic pathways

1.6 **The common use of antimicrobials:**

Antibiotics have been shown to be effective for many of the livestock diseases (Scheidy, 1951; Bunn, *et al* 1952; Roberts,1954) this is the important use as

treatment. Sawant *et al.,* 2005 stated that about 70% of antibiotics is used for disease prevention and 30% are for growth promotion. Diseases controlled by the usage of antibiotics periodically and without the usage, the frequency of infectious diseases would dramatically increase (Jones, 1992).

Antibiotics are added to animal feed at low doses (less than 200 ppm) for foremost reasons. Firstly, they are known to increase the growth rate and improve the feed utilization. Secondly, they are known to minimize mortality and morbidity from subclinical infections by preventing frequent animal diseases. How exactly antibiotics promote growth and increase feed efficiency is now not well known (Jones, 1992).

1.7 **Administration methods:**

Antibiotics are administered to animals by using injections (intravenously, intramuscularly, or subcutaneously), orally in feed or water, typically on the skin and by using intramammary and intrauterine infusions (Mitchell *et al*., 2002). Antibiotic medication through the feed represents a convenient and effective means of treating certain specific disease conditions (Luther and Hawley., 1953).

1.8 **Antibiotic groups:**

There is some antibiotics groups we will focus some light on them

1.8.1 **Tetracyclines**

Tetracycline used to be discovered in 1945 from a soil bacterium, it is a natural compound of the genus *Streptomyces* by Benjamin Duggar (Sanchez *et al*., 2004). Tetracycline antibiotics are close derivatives of the polycyclic naphthacene carboxamide. Some of them are the product of bacteria called *Streptomyces*, whereas others are semisynthetic products (Nollet, 1992). It is a wide-spectrum

antibiotic with bacteriostatic activity against each gram-positive and gram-negative bacterium, such as the species of *Spirochete*, *Actinomyces*, and *Mycoplasma* (Morshdy *et al*., 2011; Slana and Dolenc, 2013).

Oxytetracycline is used for the treatment of respiratory and gastrointestinal infections (Haagsma and Mengelers, 1989; Riviere and Spoo, 1995), but it is poorly metabolized in target animals and excreted in its parent form, due to its excessive water solubility (Tajik *et al.*, 2010). This could leave some residues inside the body and it could cause allergic reactions in some individuals if consumed for a long time (Mcintyre and Choonara, 2004). It is eliminated in the urine and feces (Riviere and Spoo, 1995).

A maximum residue limit (MRL)/tolerance of 100 μg kg-1 in the muscle of all food-producing species has been officially established through the EU (Slana and Dolenc, 2013).

Tetracyclines (e.g., tetracycline, doxycycline, chlortetracycline and oxytetracycline) represent about half of all antibacterials used in animal production due to their low cost and are consequently one of the most commonly detected antibacterials in foods (Lynas *et al*., 1998; Kennedy *et al*., 2000; Oka *et al*., 2000; Guigere, 2006).

They are largely used all over the world as oral or parenteral medications and as additives in feed for animals promoting food production (Nollet,1992). Only chlortetracycline and oxytetracycline are licensed among 10 antibiotic compounds as growth promoters for livestock in the USA (Meyer *et al*., 2000).

The consuming of the food that includes low ranges of tetracyclines for long intervals can motive the spread of drug-resistant micro-organisms (Cinquina *et al*.,2003). The tetracyclines are acknowledged for their capacity to cause acute

allergic reactions and hence is a foremost concern as residues in food products (Botsoglou and Fletouris, 2001). Also, it has been reported that some tetracycline residues can undergo heat degradation for the duration of cooking processes and produce toxic metabolites, which may additionally have nephrotoxic properties (Fedeniuk, 1988; Rose *et al*., 1996; Moats, 1999). Tetracyclines are rapidly eradicated from edible tissues, thus in most cases, a withdrawal period of solely 24 hours is generally enough for concentrations to fall under the tolerance stage (McEvoy *et al*.,1994; Lynas *et al*., 1998). In bone tissue, however, most tetracyclines bind nearly irreversibly (Korner *et al*., 2001; Zakeri and Wright, 2008) and bone meal used from treated animals can result in an unintentional source of residues in the animals.

1.8.2 **Quinolones or fluoroquinolones**

High concentrations of fluoroquinolones are found in organs of excretion (Walker, 2000). Enrofloxacin de-ethylated to ciprofloxacin as the main metabolite (Küng *et al*., 1992; Kaartinen *et al*., 1995 and 1997; Anadón *et al*., 1999), and a remarkable activity is due to the metabolite.

The well-known forms of quinolone used oxolinic acid, nalidixic acid, flumequine, enrofloxacin, sarafloxacin, danofloxacin, orbifloxacin, marbofloxacin, gatifloxacin, grepafloxacin (Eisele *et al*., 2009) have been widely used in animal production. These compounds are associated with potential damage to articular cartilages and tendons (particularly in children), as well as myalgia (Eisele *et al*., 2009) and neurological disorders (depression, confusion, anxiety) (Takizawa *et al*., 1999a, 1999b; Ambrose *et al*., 2007; Kiangkitiwan *et al*., 2008). Some of these antibacterials, such as enrofloxacin, danofloxacin, and orbifloxacin, have been prohibited from any use in food animals due to their feasible role in the development of bacterial resistance (FDA, 2005a). Concerns regarding resistance

associated with fluoroquinolone use in animal production were first expressed by way of Elam and co-workers (1951) and are an important factor in the regulation of these compounds (Swann, 1969; Piddock, 1996; NRC, 1999; Tollefson and Flynn, 2002; Angulo *et al*., 2004; Grugel and Wallmann, 2004; Turnidge, 2004; FDA, 2010; Sharfstein, 2010).

1.8.3 **Chloramphenicol**

Chloramphenicol is broadly used in poultry industries, due to its broad-spectrum antimicrobial activity as properly as its remarkable penetration into the tissues (Kaneene, 1997). Chloramphenicol is an antibiotic naturally produced via soil organisms of the genera Streptomyces and for this reason, animals can also unintentionally be exposed to small amounts of this compound (Wongtavatchai *et al*, 2005).

This antibiotic is in a class in itself. It is a nitrobenzene derivative of dichloroacetic acid (Kirk, 1978).

A plastic anemia can occur in susceptible individuals exposed to concentrations of chloramphenicol that might remain as residues in edible tissues of chloramphenicol-treated animals (Settepani, 1984). This disease appears in approximately 1:10,000 to 1: 45,000 humans who acquire chloramphenicol (Papich and Riviere, 2001).

Although it is recognized to exert several side effects in humans such as bone marrow depression and grey syndrome in newborns (Kaneene,1997), also may cause neuritis, encephalopathy with dementia and ototoxicity. Chloramphenicol and its metabolites could be genotoxic (Lozano and Arias, 2008).

Chloramphenicol deadly impact in human has led to restrictions on the utilization of this drug through Food and Drug Administration (FDA) and regulations of

WHO have banned chloramphenicol utilization in animals (Yorke and Froc, 2000 ; Lara *et al* 2012; Mesgari *et al.*, 2012) because therefore, even low concentrations of this antibacterial with the aid of systemic (such as from food) or in topical exposure can motive toxic effects. Because there is no safe awareness for this drug (Black, 1984; Settepani, 1984; Norcross and Post, 1990; Page, 1991; Cooper *et al*., 1998; NRC, 1999; Codex Committee, 2004; 21CFR530, 2010).

1.8.4 **Aminoglycosides**

Aminoglycosides are used mainly in the treatment of infections caused by way of aerobic, gram-negative microorganism (Isoherranen and Soback., 1999). It is eradicated unchanged by way of renal excretion (Sande and Mandell, 1980; Prescott, 2000e).

All contributors to this team have amino sugars in glycoside linkage. This group includes the streptomycins, neomycin, kanamycin, paromomycin gentamycin, and amikacin. (Kirk, 1978).

Aminoglycosides are generally known for their ototoxic and nephrotoxic properties in both animals and humans (Drusano *et al*., 2007). Damage to the ear, primarily the vestibular and cochlear nuclei, has been particularly noted in the case of children uncovered to these compounds during pregnancy (Al-Aloul *et al*., 2004; Matz *et al*., 2004; Selimoglu, 2007). The incidences of mild to severe renal effects in patients treated with these antibacterials have been reported at around 10-25% (Taber and Pasko, 2008). Additionally, allergic reactions associated with these compounds have been reported (Tinkelman and Bock, 1984; Faridah *et al*., 2004). The Federal authorities have imposed very low tolerance tiers and long withdrawal periods for these compounds in food products, particularly for neomycin, because these compounds tend to remain in the ear and kidneys for

prolonged periods of time, sometimes months, after treatment (Stead, 2000; Gehring *et al*., 2005).

1.8.5 **Sulphonamide**

Sulphonamides are reported, the first group of antibiotics used in therapeutic medicine, and they still play an important role in medicine and veterinary practice (Eyssen *et al*., 1971). In veterinary practice, Sulphonamides have been benefited as antibiotic sellers in veterinary practice for several decades and are the fifth most widely used group in veterinary antibiotics in European Union countries (Boxall *et al*., 2002: Van Rhijn *et al*., 2002). Sulphonamides show antimicrobial activity with trimethoprim, that is why they are frequently co-administered with this compound. Among many Sulphonamides that has been defined, only a few are approved for animals as veterinary medicine. (Van Rhijn *et al*., 2002).

The most frequently used sulphonamides are sulfadiazine, sulfadimidine, sulfamethoxazole, sulfadoxine, and sulfadimethoxine (Van Rhijn, *et al*. 2002). Sulfamethazine is used therapeutically to treat infections, to control the spread of diseases as a preservative, to expand feed fertility and to increase growth rate (Ko, *et al*., 2000, Furusawa, 2000). Sulphonamides and trimethoprim are used for the treatment of respiratory and alimentary tract infections (Boison *et al*., 1996). sulphonamide tissue residue concentrations from porcine urine and bile concentrations (Randecker *et al*., 1987; Fodey *et al*.,1997) and bovine plasma concentrations (Lee *et al*., 2001b).

Unfortunately, exposure to sulfonamides can induce adverse reactions in people including photosensitivity, thyroid toxicity (particularly caused through sulfadimidine), poisonous epidermal necrolysis (Stevens-Johnson Syndrome and the extreme structure of the disease called Lyell Syndrome), urinary tract disorders,

porphyria, hematopoietic disorders, onset of fetal hyperbilirubinemia and kernicterus throughout late pregnancy, as properly as teratogenic effects (Dunn, 1964; Swarm *et al*., 1973; Peters *et al*., 1990; Mitchel, 1994; NRC, 1999; Slatore and Tilles, 2004; Wang *et al*., 2006).

It has been reported that sulfonamides can induce hypersensitivity reactions in approximately 10% of the general population and about 60% of patients with human immunodeficiency virus (HIV) (Dewdney *et al*., 1991; Dayan, 1993; Berends *et al.*, 2001). Sulfonamides have a number of characteristics that increase their potential for leaving residues in handled animals. For example, these drugs tend to be eliminated unchanged from the body and be disseminated to untreated animals through feed, water or environmental contamination. Furthermore, as these drugs tend to persist for lengthy periods of time in the environment this can lead to an underestimation of the exposure hazard (Bevill, 1984, 1989; Van Dresser and Wilcke, 1989; McCaughey *et al*., 1990; Waltner-Toews and McEwen, 1994a, 1994b; Riviere and Spoo, 2001; Buur *et al*., 2006; Agwuth and MacGowan, 2006). Sulfonamides can additionally persist at injection sites for over 30 days after application, in contrast to other antibacterials that disappear from the injection site within 24 hours such as neomycin, tylosin and oxytetracycline (Galer and Monro, 1996; Van Donkersgoed *et al*., 1999; Reeves, 2005, 2007).

Studies have shown that Sulphonamides are additionally capable to impede cancerous cell agents (Stawinski *et al*., 2013; Xu *et al*., 2014). The withdrawal time for Sulfamethazine is estimated to be fifteen days (Ko *et al*., 2000, Furusawa, 2000). Data from a sulfamethazine residue program recommended that 25% of violations were due to the insufficient cleansing of feed mixers (Guest and Paige, 1991). Within the EU, the maximum residue limit in milk has been determined to be one hundred ppb. Some countries do now not approve Sulphonamides in food

for human consumption and determination of sulphonamides requires methods that have low detection levels (Van Rhijn, *et al*. 2002).

1.9 **Risk Factors for the Development of Residue in Food-producing Animal**

Veterinary drug residues are one of the important problems for food contamination (Doyle, 2006). VMPs and agricultural chemical compounds used according to label directions should not result in residues at slaughter. However, possible reasons for such residues include: Not following recommended label directions or dosage (extra-label two usage); not adhering to recommended withdrawal times; administering too large a quantity at a single injection site; use of drug-contaminated equipment, or failure to top clean equipment used to combine or administer drugs; dosing, measuring, or mixing errors; allowing animals get admission to spilled chemical substances or medicated feeds; animal effects- age, pregnancy, congenital, illness, allergies; chemical interactions between drugs; variations in water temperature for fish species; environmental contamination; and improper use of agricultural chemical substances such as pesticides (CFIA, 2014) .Veterinary drugs or VMPs residues usually accumulate in the liver or kidney as a substitute than other tissues. It has been noted that different residue levels can be located in different tissue positions such as site and route of administration (Doyle, 2006). The most probable cause for drug residues may additionally results from human management, such as improper usages, inclusive of extra-label or illegal drug applications. However, the most obvious cause for unacceptable residues might be due to failure to hold to the withdrawal period including the use of overdose and long-acting drugs (Beyene and Tesega, 2014).

1. Age of animal: Weaning reputation and, to a lesser extent, the age of the animal have an effect on drug disposition (Schwarz, 2014). For instance, the study conducted on comparisons of the pharmacodynamics of norfloxacin nicotinate

between weaning and unweaned calves published that the distribution of the drugs did not vary between the groups of calves, but the total body clearance time was accelerated in weaned calves, maybe due to elevated weight from the presence of rumen fluid (Gips and Soback., 1996). Calves fed grain had shorter clearance times (approximately four days) for sulfamethazine than unweaned calves. The removal half-life of tinidazole is shorter in unweaned calves than in adult cows, while the removal half-lives of apramycin is longer in calves than in adult cattle, possibly due to the immaturity of the drug clearance system (Kaneene and Miller,1997).

2. Feeding: Diet can affect the bioavailability of drugs (Bushra *et al*.,2011). For instances, study conducted to determine the effects of eating regimen content on the bio-availability of orally administered fenbendazole to cattle and Indian buffalo and fed dry hay either with or without fresh green herbage showed that animals receiving feed containing fresh herbage had lowered bio-availability of the drug. Fenbendazole stays in the rumen and is progressively released with digest, and the presence of fresh herbage increases intestine activity and the waft fee of digesta, which depletes the available stores of fenbendazole in the rumen. In regard to feeds, actual gut contents can also affect drug uptake two and pharmacodynamics (McConville *et al*.,1995; Kaneene and Miller,1997; Toutain *et al*., 2010).

3. Disease status: the disorder status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues (Boothe and Reevers ,2012).is can occur either when the disease affects the metabolic system (and hence drug metabolism), or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues. For example, cattle with acutely infected mastitis quarters, apramycin penetrates these areas of the body, and concentrations of the drug have been observed at ten times over the level recorded from cows without mastitis. Ketoprofen levels in milk increase during

clinical mastitis the place there is an influx of serum components into the udder. In calves with experimentally caused fasciolosis, the removals half-lives of antipyrine used to be slightly increased, however, used to be slightly decreased for erythromycin and statistically significantly reduce for oxytetracycline. The proposed mechanisms for these changes were the modifications in liver characteristic by fasciolosis, which changed the processing of drugs thru the liver (Korsrud *et al*.,1993).

4. Pharmacokinetics: Is a term referred to the motion of drug into, thru and out of the body: the time course of its absorption, bioavailability, distribution, metabolism, and excretion (Boothe and Reevers ,2012).

5.Absorption: It is described as the process, which a compound passes from its site of administration into the bloodstream (Boothe and Reevers ,2012). Absorption is influenced through many factors such as the properties of cell membrane, drug properties and route of administration and physiopathological state of the animal. An indication of the rate of drug absorption is obtained from the peaks plasma concentration (Cmax) and time reaching the maximum concentration (Tmax) (Riviere *et al*.,1991; Boothe and Reevers,2012).

6.Distribution: It is the process whereby a drug is transported to all the tissues and organs. After entering the systemic circulation, in something route of administration, drugs are conveyed during the physiques and reach their site of actions. There are four important factors responsible for the extent and rate of distribution. These are the physicochemical properties of the drug, the concentration gradient established between the blood and tissue, the ratio of the blood of flow to tissue mass, and the affinity of the drug for tissue constituents and serum protein binding. Only the fraction free form (unbound) of the drug is capable of exiting the circulation to distribute through the body and exert

undertaking at the site of action. The parameter, which defines the process of distribution, is the volume of distribution (Botsoglou and Fletouris, 2001).

7. Metabolism (Biotransformation): It is the principal mechanism of elimination for the transformation of drugs or xenobiotics into metabolites of the chemical reaction. Hepatocytes play an extremely vital role in the metabolism of drugs and xenobiotic-compounds that are foreign to the body, some of which are toxic. The kidneys are responsible finally to dispose of these substances, but for effective elimination, the drug or its metabolites must be made hydrophilic (polar, water-soluble), that because re-absorption of a substance by the renal tubules is dependent on its hydrophobicity. The extra hydrophobic (non-polar, lipid-soluble) substance is, the extra likely it will be reabsorbed. Many drugs and metabolites are hydrophobic, and the liver converts them into hydrophilic compounds through using the classes of enzymatic pathways of biotransformation; phase I (non-synthesis) and phase II(conjugation). Phase I corresponds to functionalization processes including oxidation, reduction, hydrolysis, hydration and isomerization reactions. Phase II reactions involve conjugations of the drug or section I metabolite with the endogenous substrates such as glucuronic acid, sulfate, acetates and methyl group. Although some drugs are eliminated from the body by using uncharged, most drugs undergo metabolism the place the liver is the essential organ of reaction. In addition, the liver's function may additionally change the drug's shape to be inactive and easy to excrete but some drugs may be converted to an activating form (Riviere *et al.*,1991).

8.Excretion: The process of excretion by which the parent drug or its metabolites are removed from the body fluids. The kidney is the most important site of drug excretion. There are three renal mechanisms; glomerular filtration, carrier-mediated proximal tubular secretion and pH-dependent, passive tubular resorption

in the distal nephrons. Renal insufficiency usually significantly affects drug excretion. The systemic clearance and removing half-lives are necessary parameters referring to the basic rate of removing (metabolism and excretion). Although most compounds are excreted primarily through the renal, some pills are partly or definitely excreted thru the bile. It has been stated that there is a full-size species variant among animals in their usual capability to excrete capsules in the bile; example, hen is characterized as excellent biliary excretes, whereas sheep and rabbit are characterized as average and bad, excretes (Riviere *et al*., 1991).

9. Extra-label drug use (ELU): Referred to the use of an approved drug in a manner that is not in accordance with the accepted label directions. ELU takes place when a drug only accepted for human use is used in animals, when a drug permitted for one species of animal is used in another, when a drug is used to treat a circumstance for which it was now not approved, or the use of drugs at levels in excess of encouraged dosages (Weaver,1992; Boothe and Reevers ,2012). For instances, the use of phenobarbital (a drug only approved for use in humans) to treat epilepsy in dogs and cats; the use of ivermectin in dogs and cats (an antiparasitic only authorized for use in cattle); and the use of enrofloxacin solution as a topical ear medication (only approved for use as an injection) are the common ELU in veterinary medication (Gillian ,2003). There are conditions for ELU in food animals. For example, when thinking about ELU of an authorized human drug in food animals: the veterinarian ought to have medical rationales for the use; the veterinarian may not use an approved human drug if an animal drug permitted for use in food-producing animals can be used instead for the specific ELU; and if scientific facts on the human food safety aspect of the use of the drugs in food-producing animals is not available, the veterinarian have to take excellent measures to guarantee that the animal and its food products will not enter the human food

supply(Gillian,2003).The families of drugs (both in animals and humans), and components currently prohibited for ELU in all food producing animals (including horses supposed for human food) are chloramphenicol, Clenbuterol, diethylstilbestrol (DES), dimetridazole, ipronidazole, furazolidone, nitrofurazone, sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromo-methazine, and sulfamethoxypyridazine, fluoroquinolones, and glycopeptides) (CFR.,2006).

10.Improper withdrawal time: withdrawal time (also known as the depletion or clearance period) is the time for the residue of toxicological concern to reach a safe concentration as defined by means of the tolerance. Depending on the drug product, dosage form, and routes of administration, the withdrawal-time might also vary from a few hours to several days or weeks. It is the interval necessary between the last administration to the animals of the drug under regular situation of used and the time when treated animal can be slaughtered for the production of safe foodstuffs (Kaneene and Miller, 1997).

1.10 Incidence of veterinary drug residues: In many countries, VMPs can also be used indiscriminately for the treatment of animal diseases or they might also be used as feed additives for domestic animals (Jacela *et al*.,2009). Different studies have been conducted by Zuo *et al*.(2012) in Pennsylvania . Babapour *et al*.(2012) in Iran to show the incidence rate of VMPs residue in different parts of the world. The research revealed that low level of heavy metals and gentian violet residue from catfish was once detected (Zuo *et al*., 2012; Ozbay *et al*,.2013). Other studies conducted in Nigeria additionally revealed the detection of antimicrobial drug residues in commercial eggs (Kehinde *et al*.,2012), in meat from slaughtered cattle(Ibrahim *et al.,* (2009) .Furthermore, oxytetracycline and penicillin G from milk (Desalegne *et al*.,2014), and tetracycline from cattle beef(Addisalem *et al*

.,2012) were additionally detected in Ethiopia.the ongoing threat of antibiotic contamination is one of the biggest challenges to public health that is faced with the aid of the human population worldwide. Such residues are spreading rapidly, irrespective of geographical, economic, or legal differences between international locations (Darwish *et al*.,2013).Additionally, the study reported in 2004 by EU revealed that the majority of residues confirmed in animals were antibacterial agents (EC., 2010).Currently, the joint FAO/WHO Expert Committee on Food Additives (JECFA) has also reported a range of veterinary drugs and other environmental substances residues in a series of working documents. Additionally, the JECFA has been participating in further evaluating the safety of residues of veterinary drugs in food and in establishing acceptable daily intakes (ADIs) and propose maximum residue limits (MRLs) for substances when they are administered to food-producing animals in accordance's with good veterinary practice in the use of veterinary drug (JECFA ,2013).

1.11 The potential effect of veterinary drug residues on public health: Drug of low-level of contamination generally can not generate a violation problem on public health. However, extensive use of drugs can also increase the risk of an adverse effect of residues on the customer including the occurrence of antibiotic resistance (Samanidou and Nisyriou,2008; Beyene and Tesega, 2014) and Therefore, prudent use of drugs in the manner of preventing feed contamination is necessary (FSAI, 2007).

1.11.1 Development of drug resistance: Human health can both affect through residues of drugs in food of animal origin, which may add cause direct side effects (Beyene and Tesega ,2014), or indirectly, through selection of antibiotic resistance determinants that may additionally spread human pathogen (Samanidou and Nisyriou,2008;Landers *etal*.,2 012 ; Chang *et al*.,2014).

The resistant microorganism can get access to human, both via direct contact (Chang *et al*., 2014) or indirectly via milk, meat, and or egg. As the bacteria of animal origin, they may additionally either colonize human endogenous flora or superimpose and additional load to the-reservoir of resistance genes already present in man. The potential for animal to human transfer of resistance exists. Clearly, the use of antibiotic in livestock production has been associated with the improvement of human antibiotic resistance (Landers *et al*.,2012; Chang *et al*.,2014). The animal fed with the low prophylactic level of antibiotic may enhance bacteria-evolving resistance to this antibiotic during the preparation or consumption of food of animal origin (NRC,1991). It has been documented that human develop drugs resistant microorganisms such as *Salmonella*, *Campylobacter*, and *Staphylococcus* from food of animal origin (Chang *et al*.,2014). Examples of drugs that have been shown to cause the growth of resistant bacteria in the food of animal are fluoroquinolones and avoparcin. The resistance of microorganisms, arising from sub-therapeutic makes use of penicillin, tetracyclines, and sulfa drugs; in agriculture is suggested with the aid of the WHO to be a high priority issue (NRC, 1991).

1.11.1.1 The Danger of Antibiotic to Human Resistance:

The major public health concern is the increasing occurrence of strains of bacteria resistant to antibiotics. Some antibiotics are beginning to lose their effectiveness, thereby making it difficult to treat some common illnesses. This is due to the over-exposure of humans to antibiotics. This phenomenon has resulted in the removal or restriction on the use of certain antibiotics. The use, and misuse, of antibiotics in treating diseases in humans is the high reason for the development of resistant bacteria. Continuous use of antibiotics can result in the emergence of a new generation of organisms, which possess genes with resistance to sure antibiotics

(McGrane, 2000). In humans, microbial resistance is an important problem in a wide variety of infections of the skin, respiratory, genitourinary and gastrointestinal tract (McEwen, 2006).

1.11.1.2 Mechanisms of resistance:

Whether residues arrive in the food chain by using unlawful use of prohibited drugs, or inappropriately administered legal drugs, the fact stays that human ingestion of animal drug residues has been linked to elevated drug-resistance of microorganism that causes human diseases (Butaye *et al*., 2001). Bacteria have the number of ways how they become antibiotic-resistant. For example, they possess an internal mechanism of changing their structure, so the antibiotic no longer works, they develop ways to inactivate or neutralize the antibiotic. Also, the microorganism can transfer the genes coding for antibiotic resistance between them, making it possible for bacteria never exposed to an antibiotic to acquire resistance from those which have. The problem of antibiotic resistance is worsened when antibiotics are used to treat disorders in which they have no efficacy (e.g. antibiotics are not effective against infections caused with the aid of viruses), and when they are used broadly as prophylaxis rather than treatment (Bayarski, 2006)

1.11.1.3 How the resistant microorganism transmits to human?

The antibiotic-resistant microorganism is transferred to people through direct contact with animals fed with antibiotic containing feed or by way of people harboring antibiotic-resistant bacteria (Concon, 1988). Some find out about have proven that exposure to antimicrobial residues in food of animal products should end result to the transfer of resistant strains of microorganisms to humans (Nisha, 2008; Jafari, *et al*., 2000), and the Antibiotic resistance in *E. coli* is widespread globally, with agents such as penicillin that found decreasing efficacy in opposition to it

(Heritage *et al*., 2001). Generally, the resistance of microorganisms arising from sub-therapeutic of penicillin, tetracycline and sulfa drugs in agriculture is suggested with the aid of the WHO to be high priority problems (NRC, 1991).

1.11.2 Drug hypersensitivity reaction: Drug hypersensitivity is defined as an immune-mediated response to a drug agent in a sensitized patient, and drug allergic reaction is restrained to reactions mediated by IgE. An allergic or hypersensitive effect following administration of a drug (i.e., drug allergic reaction is pretty comparable to that typified by way of allergic response to protein, carbohydrate, and lipid macromolecules. Allergic reactions to drugs may include anaphylaxis, serum sicknesses, cutaneous reactions, a delayed hypersensitivity response to drugs show up to be more in many instances related with the antibiotics, especially of penicillin (Riedl and Casillas, 2003). About 10% of the human population is considered hypersensitive to an amount of a substance, such as penicillin, but in animals, the extent of hypersensitive to, the drug is no longer properly recognized (Boothe and Reevers , 2012). Certain macrolides may also in exceptional be responsible for liver injuries, induced via a specific allergic response to macrolide modified hepatic cells (Darwish *et al.* ,2013).

Drug residues additionally consist in allergic reactions and interference with indigenous human intestinal microflora. Important effects on the whole due to the presence of residual antibiotics consist in allergic reactions or the selection of a resistant microorganism that could be transferred to human beings through the food chain (Butaye *et al*., 2001).

1.11.3 Suppressing the herbal microflora:

Disruption of Normal Intestinal Flora the microorganism that usually live in the intestine which acts as a barrier to prevent incoming pathogen from being set up

and causing diseases. Antibiotics might also reduce the whole quantity of the bacteria or selectively kill some important species. The broad-spectrum antimicrobials can also adversely have an effect on a broad range of intestinal flora and consequently cause the gastrointestinal disturbance (Cotter *et al*.,2012).

In addition, the consumption of trace degrees of antimicrobial residues in food from animal origin may additionally have consequences on the indigenous human intestinal microflora, which constitutes an essential component of human physiology (Villard and Clasener, 1994). This microflora acts as a barrier against colonization of gastrointestinal tract by pathogenic bacteria (Vollard and Clasener, 1994) and has an essential role for food digestion. So, the ingestion of trace level of antimicrobials in food must take into account potentially hazardous effects on the human intestine flora (Cerniglia and Kotarski, 1999).

1.11.4 Fermentation inhibition: The contamination of Milk with antibiotic residues, and subsequently employed in the manufacture of cheese or yogurt, can result in the inhibition of cultural development, due to removing or reduction of the micro-organism critical to allow fermentation (McGrane, 2000) and this is very important economically.

1.11.5 Peptic ulcers, gastric cancer, and Dieulafoy lesion:

Isik *et al*. (2008) and Isik, *et al* (2014) noted that the antibiotics may also cause the elevated incidence of resistant *Helicobacter pylori* in the mucosa of the stomach. By this several diseases such as peptic ulcers, gastric cancer and Dieulafoy lesion occurs.

1.11.6 The lethal effect in human:

Chloramphenicol's should make a lethal impact in human has led to restrictions on the usage of this drug by way of Food and Drug Administration (FDA) and regulations of WHO have banned chloramphenicol utilization in animals (Yorke and Froc, 2000; Lara *et al*., 2012; Mesgari *et al*., 2012).

1.11.7 Cancer:

The carcinogenic effect, the term carcinogen refers to an effect produced by means of a substance having carcinogenic activity (ACS ,2014) large confusion has existed due to the fact a carcinogen applies to resources that are so varied in their qualitative and quantitative characteristics. The potential hazard of carcinogenic residues is associated to their interaction or covalently binding to various intracellular components such as proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), glycogen, phospholipids, and glutathione (Aiello, *et al*.,2005)

European Food Safety Authority (2007 issued an opinion on the impact of residues in meat and reflected that epidemiological information supplied evidence for an affiliation between some types of residues dependent cancers and meat consumption.

In light of the carcinogenic potential of drugs` residues and obvious human health risks, the European Community forbade the use of steroids as growth-promoting agents in livestock breeding (Boothe and Donald, 1998). In addition, information had furnished evidence for an association between some forms of hormone-dependent cancer and red meat consumption (Shankar *et al*., 2010).

1.11.8 Anemia

Hazards of chloramphenicol observed in association with clinical use in humans include dose-related, reversible suppression of the bone marrow, which is a circulatory collapse in children less than 30 days on excessive doses and irreversible, idiosyncratic, non-dose associated aplastic anemia (Waltner -Toews and McEwen, 1994; Maria and Mary, 2012).

1.11.9 Teratogenicity Effect:

The teratogenicity effect the term teratogen applies to drug or chemical agent that produces a toxic impact on the embryo or fetus during a critical phase of gestation. Consequently, a congenital malformation that impacts the structural and functional integrity of the organism is produced. The popular thalidomide incident involving a number of children in Europe used to be a direct testimony to the hazard that may additionally take place when such agent is administered during pregnancy (Boothe and Donald, 1998). Of the anthelmintics, benzimidazole is embryo poisonous and teratogenic when given during early stage of pregnancy because of the anthelminthic activity of the drug (Aiello*et al*.,2005; El-Makawy *et al*.,2006). In addition to embryo toxicity which includes teratogenicity, the benzimidazole drug of oxfendazole has additionally exhibited a mutagenic effect (El-Makawy *et al*.,2006).

The regular thalidomide incident involving a number of children in Europe is a direct testimony to the hazard that might also occur when such agent is administered during pregnancy (Boothe and Donald, 1998). From the anthelmintic, benzimidazole is embryo poisonous and teratogenic when given during the early stage of pregnancy because of the anthelmintic activity of the drug (Aljello *et al*., 2005).

1.11.10 Nephrotoxicosis:

Aminoglycosides given in therapeutic dosages mainly cause ototoxicosis, but may also additionally reason nephrotoxicosis, allergy, and neuromuscular disturbances. (Lozano *et al*. 2012).

1.11.11Genotoxicity and mutagenic effect:

Mutagenic effect the term mutagen is used to describe chemical or physical agents that can cause a mutation in a DNA molecule or damage the genetic component of a cell or organisms. Several chemicals, such as alkalizing agents and analogous to DNA bases, have been shown to elicit mutagenic activity (Brown, 2002). There has been increasing concern that drugs, as well as environmental chemical compounds, might also pose a potential hazard to the human population by production of genes mutagens or chromosome breakage (Boothe and Donald, 1998) that can also have adversely affects human fertility (Foster and Beecr,2014).

Chloramphenicol and its metabolites should be genotoxic (Lozano and Arias, 2008).

1.11.12 Bone Marrow Depression: Chloramphenicol is broadly used in chicken industries, due to its wide spectrum antimicrobial activity as well as its incredible penetration into the tissues. Although it is recognized to exert several aspect effects in humans such as bone marrow depression and grey syndrome in newborns (Kaneene and Miller, 1997).

1.11.13 Other Harmful Effect:

Aminoglycosides can produce damage in urinary, vestibular and auditory functions (Shaikh and Allen, 1985). Toxic and allergic reactions in humans and animals

caused by way of tetracyclines have only been observed at therapeutic doses (Berends *et al*., 2001)

1.12 How to Control Antibiotics Residues:

1.12.1 Withdrawal Periods:

The withdrawal period always printed on the label to define as the time that is required for 99% of the animals in a population (treated according to label directions) to have drug residues that are lower than accepted residue levels defined via FDA (Jones, 2014).

1.12.2 Prohibition of the Harmful Groups:

Many European countries banned using antimicrobials as food additives. Sweden prohibited in 1986 the use of additives belonging to the groups of antimicrobials in feeding stuff. Avoparcin was banned in Denmark (1995) and Germany (1996), spiramycin was prohibited in Finland (1998) because this product used to be used in human medicine, and virginiamycin used to be prohibited in Denmark (1998). Chloramphenicol, a broad-spectrum antimicrobial, was once previously broadly used in veterinary and human medicine. Reports of aplastic anemia in human beings arising from its use led to its ban in the USA and European Union (EU) in 1994. Nitrofurans, particularly furazolidone, furaltadone, nitrofurantoin and nitrofurazone for livestock production used to be totally prohibited in the EU in 1995 due to worries about the carcinogenicity of the drug residues and their potentially hazardous effects on human health (Mccalla, 1983; Vroomen *et al*., 1990; Van KotenVermeulen,1993).

Due to the emergence of fluoroquinolone-resistant microorganism particularly *Campylobacter* and *Salmonella*, the Food and Drug Administration (FDA) in 1977

banned the use of fluoroquinolones in treating poultry but the use of sarafloxacin and enrofloxacin in chicken used to be permitted, but an increase in fluoroquinolone-resistant *Campylobacter spp.* in poultry was linked to elevated incidence of infection with resistant *Campylobacter spp.* in humans. Finally, FDA in 2005 prohibited the utilization of enrofloxacin in poultry and sarafloxacin have been withdrawn via the producer, for this reason, usage of any members of fluoroquinolones in poultry species is unlawful with the aid of FDA (Davis *et al*., 2009).

1.12.3 Monitoring the animal feed stuff:

Animal feedstuffs are also analyzed for antibiotic residues. Animal finishing feed which is fed to animals in the period before slaughter, should be certified free of veterinary drugs and a specific withdrawal period is set for each antibiotic. The antibiotics commonly administered through animal feeds are the macrolides and polypeptides which are used in growth promoting and the ionophoric polyether antibiotics, used to improve feed effectivity and for the treatment of coccidiosis (McGrane, 2000).

In a recent study analysis of feedstuffs in Northern Ireland, the authors concluded that contaminated feedstuffs detected, chlortetracycline was detected in 50 % of the samples. Sulphonamides have been the next most regularly detected category9 (Lynas *et al*., 1998). Cross-contamination during milling is the prime cause of unintended antibiotic residues in feedstuffs. To stop global trade barriers related with drug residues in beef, the conditions must be applied consist of standardization of checking out methods used to observe drug residues, standardization of strategies for identifying minimum residue levels and the establishment of active surveillance programs to monitor residues (Kaneene and Miller, 1997).

1.12.4Increase the Awareness of the owners:

Although public awareness of the drug residue trouble in meals is high and various governmental agencies spend large quantities of time attempting to control this problem, residues in animal tissues are still a vital challenge today (Seri, 2013).

1.12.5 Law Force:

In the USA all animal drugs have to be accredited with the aid of FDA before they can be marketed for public use. Receiving FDA approval is a complicated and expensive process, as the drug developer should prove that the medicine is safe and fine when used at the proposed labeled dosage.

The New Animal Drug Application (NADA) must include all the possible side effects the drug can also cause and show that they can consistently manufacture the product with ingredients from safe and reliable sources. If the drug is for food animals, then withdrawal times (WDT) should be provided at the labeled dosage to ensure that the residues in meat, milk, and eggs are below ranges protected for human consumption (Jones, 2014).

The food industry and the respective authorities carry out manage programs and monitoring for drug residues in food for the good of public health and to avoid financial Loss (Cacciatore *et al*. 2004). European Medicines Agency (EMA) recommends that if the target tissue of a drug is muscle, then the regulatory authorities ought to set the WDT on the MRL for muscle (Jiang *et al*., 2006).

1.13 The challenge of regulation applications:

Differences in testing and regulations for different countries complicate the use of antimicrobials, particularly in animals that may be slaughtered for other international locations (Jones, 2014). Varies from united states to country, within a

country, and between farms, depending on Policies. Moreover, the systems used to detect antibiotics in EU countries are developed and applied by governments, companies, and farmers exhibiting many differences (Inge and George, 2006). There is no screening check currently reachable to detect the MRL of all approved drug classes of antibiotics. Everyone looks at has barriers for specificity, sensitivity, or ease of use at a slaughter facility and differences in testing and guidelines for different countries complicate the use of antimicrobials, especially in animals that can also be slaughtered for other countries (Jones, 2014).

1.14 The Minimum or Maximum Residues Limits (MRL):

According to the European Union's definition, the MRL is the maximum legally acceptable quantity of pharmacologically energetic resources or degradation products and their metabolites in foodstuffs originating from animals. The purpose of the MRL is restriction the exposure of customers to residues of medicines used in food animals, to concentrations that do not pose human health danger (Kennedy *et al.*, 2000).

WHO and FAO have set standards for the suited day by day intake and maximum residue limits in foods (FAO/WHO, 1995). In many international locations of the world, this upper level is referred to as the maximum residue degree (MRL), whilst in the United States, it is termed as tolerance (Riviere, 1999).

In March 2010, Food Safety Inspection Service (FSIS) National Residue Program (NRP) for Cattle Audit Report (24601-08-KC), concluded that the countrywide residue program was once not carrying out their mission and identified several areas of concern that need to be rectified. The FSIS, Environmental Protection Agency (EPA), and Food and Drug Administration (FDA) have been tasked to

work together to find more effective approaches to test for residues and set new acceptable residue levels (Jones, 2014).

1.15 Residue Acceptable daily intake (ADI):

It is the amount of a substance that can be ingested each day over a lifestyles time except considerable health risk. Calculation of ADI is based on an array of toxicological safety evaluation that takes into acute and long-term exposure to the drug and its potential impact (EC, 2001). If the drug is no longer a carcinogen, the no observed effect level (NOEL) of the most sensitive effect in the most sensitive species divided by a safety factor is used to determine an ADI for drug residues. the FDA will calculate the safe concentration for each edible tissue the use of the ADI, the weight in kg of an average grownup (60 kg), and the quantity of the product eaten per day in grams as follows (CFR.,2006). Safe concentration= [ADI (µg/kg/day) x 60 kg] / [Grams consumed/day].

1.16 The effect of Cooking on antimicrobial residues:

Cooking procedures can't damage the total quantities of this drug however it can only reduce their amounts and most of the residues in the boiling process are excreted from tissue to cooling fluid during the boiling process. Thus, exposure to residues can be decreased by means of discarding any juice that come from the edible tissues as they are cooked. Among the various agents affecting antimicrobial residues after the cooking process, it was once found that cooking time and temperature ought to play the most important roles (Javadi *et al.,* 2011).

1.17 Drug residue and HACCP:

The Food Safety and Inspection Service (FSIS) is a branch of the US Department of Agriculture (USDA) that monitors and investigates conditions in slaughter

plants through taking tissue samples and analyzes them for chemical residues and then it may recommend that carcasses or products found in violation are condemned and destroyed. HACCP systems are increasingly used to replace or supplement usual meat inspection and end-point sampling. Livestock producers and veterinarians must be aware of these altering necessities for farm-animal food safety. The applications of GMPs and/or HACCP at the farm or the slaughterhouse require a level of administration sophistication that normally is now not on hand in developing countries (Paul, 1997). For the high-quality prevention and control of residues establishments that slaughter sure classes of food animals must address chemical residues within their HACCP system (Bria, 2011) good manufacturing practices (GMP) (Brynes and Weber, 1996; 21CFR225 and 226, 2010). Scheduled sampling plans consist of the random sampling of tissue from healthy appearing food animals in accordance to the available intelligence reviews on the incidence and incidence of specific compounds in food products in a area (FSIS-NRP, 2008). These sampling plans are devised with the cooperation of members of the NRP-Surveillance Advisory team, that includes members from the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the Center for Disease Control and Prevention (CDC), the Animal and Plant Health Inspection Service (APHIS), the Agricultural Marketing Service (AMS), the Agricultural Research Service (ARS) and individuals from the FSIS. Based on the suggestions of this committee, the NRP proposes analytical techniques for identifying and evaluating drugs of difficulty through production class; such as:

1) Prioritizes drugs for monitoring;

2) Develops reports on the incidence of residue violations (FDA, 2005b).

In-plant generated sampling occurs when the public health veterinarian suspects that an animal or flock may additionally have been treated with a pharmacologically

active compound which may create residues. This decision to select and test a specific carcass is based on professional judgment and standards outlined in FSIS Directives 10,800.1 and 10,220.3 (FSIS, 2007). These criteria may include animal disorder signs and symptoms, producer records or results from random scheduled sampling. When an inspector generated pattern is collected, the carcass is held pending the results of laboratory testing. If a carcass is found to contain levels of residues that exceed the imposed tolerance level for that product in that specific food product, the carcass is condemned (FSIS-NRP, 2008).

1.18 Antibiotics in Human Food:

Veterinary drugs are generally used in farm animals for therapeutic and prophylactic purposes, they include many kinds of compounds which can be administered in the feed or in the drinking water. In some cases, the residues may additionally proceed from contaminated animal feedstuffs (McEvoy, 2002). Drugs in food animal species some of these drugs can be approved only in specific circumstances (therapeutic purposes) but under strict control and administration by way of a veterinarian (Van Peteguem and Daeselaire, 2004).

Rapid methods for the detection and characterization of chemical and veterinary drug residues in foods of animal origin constitutes a dynamic area in food processing, from the standpoint of food safety. Residues from these substances are present in edible tissues milk and eggs and might also exert different stages of toxicity on customers upon consumption (Suhren *et al*., 1996).

Previous studies at Sultan Qaboos University proved that a few kinds of antibiotic residues have been discovered in meat samples of poultry, sheep, and goats (Mahgoub *et al*., 2006 and Kadim *et al*., 2009). Anti-microbial activity has also

been discovered in all commercial milk products sold in Oman (Srikandakumar *et al*., 2004).

1.19 Methods of Residue detection in meat:

Methods are normally divided into screening and confirmatory, for antimicrobial residue control, some laboratories add a third intermediary stage based totally on the post-screening test which offers structural or biological activity data about the residue (Stolker and Brinkman, 2005). There are more than a few chemicals, microbiological and immunological assays used to detect antibiotic residues meat (Ramirez *et al*., 2003).

1.19.1 Screening test:

Screening method can be defined as techniques that are used to detect the presence of a substance or class of components at the level of interest. These methods have the capability for an excessive sample through and are used for large numbers of samples for potential non-compliant results. They are specifically designed to keep away from false compliant results (Sanders, 2007).

Historically, screening of antimicrobial activity in animal production began in the 60's with the problem of inhibitory activity detected via dairy industry for the duration of milk processing (yogurt or cheese) (Mitchell *et al*., 1998). Screening of animal products for veterinary drugs began mainly with the dairy enterprise to overcome issues associated to fermentative dairy production, from 1970s regulatory screening of slaughtered animals was started (Mariël,2007). Two kinds of analytical techniques are commonly used, the screening techniques that consist of microbiological tests (Disc assay, modified Premi and Delvotest methods) (De Wasch *et al*., 1998; Salman *et al*., 2012 and Hind. *et al* .2012).

1.19.2 Bio-based screening methods

Bio-based screening methods used for the detection of antibiotics in products of animal origin have been reviewed (Popelka *et al*., 2004; Pikkemaat, 2009; Cháfer-Pericás *et al*., 2010; Meng and Xi, 2011). The most commonly applied bio-based screening techniques for antibiotics are microbiological inhibition assays, immunoassays and reporter gene assays (Bovee and Pikkemaat, 2009).

Preparation procedures and handlings of samples, especially solid and heterogeneous foods like meat, kidney or liver, are very important in order to make sure better sensitivity of the screening assessments (McCracken *et al*., 2000).

In general, they do not require very laborious sample pretreatment steps. They might also detect the presence of an antibiotic residue or a class of antibiotics and usually allow excessive sample throughput. Biologically based totally assays, regularly employed for screening purposes, consist of microbial inhibition assays, immunoassays, enzyme and receptor assays (McGrane, 2000).

1.19.3 Biologically based assays:

1.19.3.1 Microbial inhibition assays

The microbiological methods used for detecting antimicrobial residues in foodstuffs are primarily based on inhibiting microbial growth, microbial receptor activity, and enzymatic reactions. Microbial inhibition assays involve culturing a microorganism from a standard strain, usually, *Bacillus stearothermophilus*, *Bacillus subtilis, Bacillus cereus*, *Micrococcus luteus*, *Escherichia coli, Bacillus megatherium*, *Sarcina lutea and/or Streptococcus thermophilus* (Schumacher *et al*., 2001). Microbiological methods are quite suitable for the detection of antimicrobial residues specifically as they are less pricey than immunochemical

and chromatographic methods) and are able to screen a large number of samples at minimal cost (Pikkemaat, 2009). Microbial inhibition assays tend to be nonspecific in nature, therefore they are used as screening methods to identify samples which may additionally include antibiotic residues and these query high-quality samples are then subjected to similar analysis. They are many times employed for routine, qualitative analysis, due to their speed and ease of use (McGrane., 2000). Microbiological inhibition assays are based totally on a reaction between a microorganism and the antibiotic existing in the sample. Different inhibitory tests were developed to screen special animal products (Popelka *et al*., 2004).

1.19.3.2Charm test

The Charm I and Charm II checks are microbial receptors or antibody assays for the detection of antimicrobial drugs (Toldra and Reig, 2006). Separate tests for the antibiotic drug families' ß-lactams, macrolides, Sulphonamides, tetracyclines, and chloramphenicol are available. The tetracyclines and chloramphenicol assays are antibody assays and the remaining are microbial receptor assays. A binding reagent (a microbial cell with unique receptors for the antibiotic in question or, for tetracyclines and chloramphenicol, an antibody specific to the antibiotic) is added to the sample (McGrane, 2000).

The test employs C14 or H3 radio labeled antibacterial to compete for the binding sites. If the antibiotic is present it will bind to the receptors on the microbial cell (or antibody) and prevent the binding of radiolabelled antibiotic, which is added subsequently. Therefore, the more radiolabelled antibiotic detected the lower the concentration of antibiotic in the sample (Navratilova, 2008).

Detection of sulphonamides, streptomycin and erythromycin antimicrobial residues in suspected meat samples the usage of the Charm II receptor assay, was once

compared with the results obtained using thin layer chromatography or liquid chromatography; the comparison showed that Charm II test is a suitable alternative, with a decrease limit of detection. Also, results showed the incidence of false positives to be higher the use of the Charm II test.

1.19.3 .3The Charm II assay:

Korsrud and De Ruig *et al.* (1989) described the detection of antimicrobial residues in suspect meat samples the usage of the Charm II receptor assay. Sulphonamides, streptomycin, and erythromycin had been the antibiotics of interest. They compared the results with these obtained the usage of thin layer chromatography or liquid chromatography and confirmed the Charm II test to be an acceptable alternative, with a lower limit of detection. The results showed the incidence of false positives to be higher, using the Charm II test; however, this may also be due to the lower sensitivity of the Charm II assay (McGrane, 2000).

The estimated detection sensitivities of the Charm II test assay, were 10 ppb for penicillin G (which has an MRL of four ppb in milk), 200 ppb for gentamicin (which has an MRL of 100 ppb in milk), and 300 ppb for tetracycline (which has an MRL of 100 ppb in milk) (McGrane, 2000). The most disadvantage of charm tests is the price and the need for waste disposal (Toldra and Reig, 2006).

1.19.3.4 Cite Probe (3-lactam) kit:

This test is primarily based on the binding of P-lactam antibiotics via a penicillin-binding protein on a membrane. An absorbance reader is used to assess the color exchange which indicates if the sample is positive or negative (Color et al., 1994).

1.19.3 .5 The Lactek (P-lactam) kit:

It is primarily based on the principle of enzyme-linked immunosorbent assay (ELISA), where antibodies are coated inside a tube and response measured as optical density (Boison *et al*., 1995).

1.19.3 .6 The tube and plate test:

The tube and plate tests are the most common formats for this kind of screening assays (Berendsen, 2013). The tube check consists of a growth medium inoculated with a bacterium, supplemented with a pH or redox indicator. If no specific antibiotics are present, the bacteria begin to grow and produce acid, which will cause a detectable color change. If antibiotics are present that inhibit bacterial growth, no color change will occur (Hoff *et al*., 2011).

1.19.3 .7 The plate test assay:

The agar diffusion assay can be carried out as a tube or plate assay (Hewitt, 1977). An agar gel capable of supporting the growth and multiplication of micro-organisms is inoculated uniformly with a suspension of a test organism that is sensitive to the antibiotic(s) under test. When an aqueous solution is placed in contact with the gel, any antibiotics present may also diffuse from the solution into the gel. The antibiotic will inhibit the increase and multiplication of the micro-organism and so a clear zone will appear in the agar around where the sample was applied. This is termed the zone of inhibition (Hewitt, 1977). The size of the sector is proportional to the concentration of the antibiotic present. Penicillins, tetracyclines, aminoglycosides, and cephalosporins have all been detected by the use of this method (Cullor *et al*., 1994).

The plate test consists of a layer of Nutrient Agar inoculated with bacteria and the samples are brought onto the surface. If no specific antibiotics are present, the bacteria start to grow throughout the plate. If a specific antibiotic is present, no bacterial growth will occur around the sample, which can be observed from the microorganism free inhibition zone (Berendsen, 2013).

1.19.3 .8 Plate assay method:

Sterilized nutrient agar plates were inoculated with a loop full of a freshly prepared suspension of every bacterium. An incision was made in the tissue sample, then using clean sterile forceps, a sterile paper disc was once placed into the incision and left till it was soaked and then the disc was transferred and placed on the agar surface. The plates have been then inverted and incubated at 37- 38°C for18- 24 hours. The presence of antibiotic residues in the sample was once indicated by way of the presence of an inhibition area of a diameter of 2mm or more. The absence of antibiotic residues used to be indicated by using the absence of inhibition zone around the growth or the presence of a sector of less than 2mm (Tajik *et al*., 1998 and WahabAlla *et al*., 2011).

- **Factors may influence sensitivity results of agar diffusion methods:**

Several factors may influence sensitivity results of agar diffusion methods besides the type of the test organism. It has been reported that the results might be affected by, e.g., the composition of the sample tested, agar thickness, concentration of the test strain spores in the medium, technique of sample application, agar pH, evaluation of results, etc (Navratilova *et* al., 2010).

1.19.3 .9 Advantages Plate assay method:

1-Some of these tests are available as kits with a high sample throughput. They need limited laboratory capacity to ensure reproducible conditions of application.

A few of them need a more experienced laboratory that is able to produce a medium and a bacterial suspension. They are widely used to perform residue control and self-control by industry (Pikkemaat, 2009).

2-An important advantage, compared to immunoassays and instrumental methods, is that microbiological tests can detect any antibiotic compound that shows antibacterial activity (Picó and Barceló, 2008).

3-Moreover, they have the potential to cover the entire antibiotic spectrum within one test (Pikkemaat, 2009).

1.19.3 .10 Disadvantages Plate assay method (Berendsen, 2013):

1-The most important drawbacks of the microbiological tests are their lack of selectivity, especially the tube test.

2- Relatively high detection limits.

3- Long incubation time.

4-As a result, microbiological inhibition assays are now not appropriate for detection of banned antibiotic compounds like chloramphenicol.

1.19.3 .11 The Swab Test on Premises (STOP):

Using of tissue that is macerated with the swab, the swab is then incubated on medium inoculated with *Bacillus subtitles* and with a disk containing an antibiotic for 16-24 hours (Korsrud *et al*., 1998).

1.19.3. 12 The Calf Antibiotic and Sulfa Test (CAST):

By using of kidney fluid collected by way of making an incision in the kidney and absorbing fluid, placing the fluid with *Bacillus megaterium* in the medium and

incubat for 16-24 hours. For both the STOP and the CAST, a zone of inhibition around the swab demonstrates the presence of a microbial inhibitor in the accumulated sample (Jones, 2014).

1.19.3 .13 The Fast Antimicrobial Screen Test (FAST):

Using of *B. megaterium* and the same medium as the CAST test. However, the medium is supplemented with dextrose and bromcresol purple, which allows the bacteria to develop at a faster rate, for this reason reducing the required incubation time from 16 to 6 hours (Jones, 2014).

1.19.3 .14 Disadvantages:

None of these approved screening tests (FAST-CAST-STOP) in the U.S. is sensitive enough to detect chloramphenicol or sulfa drugs (Jones, 2014).

1.19.3.15 The Live Animal Swab Test (LAST):

Screening of urine and plasma anti mortem for drug residues. The LAST was adapted from STOP assay but they use a higher concentration of *Bacillus subtilis* spores in the assay (Jones, 2014).

1.19.3 .16 Delvotest:

Based on microbial inhibition, enzyme inhibition assays, such as "Penzyme", and bacterial metabolism inhibition assays (Moats, 1999).

1.19.3 .17 The evaluation of inhibition kits assay:

Korsrud *et al*. (1998) recently evaluated a large quantity of microbial inhibition kit assays. They concluded that while the ideal test kit does not exist, due to limitations in sensitivity, specificity, and ruggedness, they ranked the New Dutch

Kidney Test (One-plate test) and the "Swab Test on Premises" (STOP) highest with appreciate to cost, labor, and specificity.

1.19.3 .18 Four -plate method (EU4pt):

This method was first published in 1980 (Bogaerts and Wolf, 1980) and is based on three *Bacillus subtilis* based test plates and a fourth *Micrococcus luteus* plate (ATCC 9341, renamed to *Kocuria rhizophila* (Tang and Gillevet 2003). Within the EU this method served as a reference till it used to be decided to determine acceptable residue limits on an extra scientifically based totally approach (the effectuation of Council Regulation (EEC) 2377/90 (EC, 1990) and MRLs have been set at degrees past the detection functionality of this method.

Although the EU4pt is generally recognized not to be sufficiently sensitive, it is still used in many laboratories (Gaudin *et al*., 2008; Berendsen *et al*., 2010)

Recently the Premi Test and a similar test, the Explorer (Zeu- Inmunotec), have gone through an extensive validation carried out by way of the EU Community reference laboratory (Gaudin *et al*., 2008, Gaudin *et al*., 2009).

1.19.3 .19 Method:

The EU4pt was performed tests essentially similar to Bogaerts and Wolf (1980). Test agar pH 6 (Merck), Antibiotic medium II (Difco) (adjusted to pH 7.2, supplemented with trimethoprim to a final concentration of 50 μg l-1), and Test agar pH 8 (Merck), were inoculated with about 104 two CFU/ml *B. subtilis* BGA spores (Merck) and Test agar pH 8 (Merck) was inoculated with 104 CFU ml-1 *K. rhizophila* ATCC 9341. A volume of 105 ml of the inoculated growth media was poured in 245 x 245 mm square Petri dishes, resulting in a layer of 2 mm thickness.

Samples have been prepared by means of freezing a thin slice of muscle briefly at -80ºC and subsequently take out disks, using a cork borer with a diameter of 4 mm. Meat disks have been placed on each of the 4 test plates, with a maximum of 24 samples per plate. As a quality control on every plate a paper disk impregnated with either 10 IE penicillin, 5 µg sulfamethazine, 0.5 µg dihydrostreptomycin or 0.5 µg tylosin was once added (by adding 100 µl of a clean 10x stock).

Test plates had been incubated for 14-16 hr at 30ºC (*B. subtilis*) or 37ºC (*K. rhizophila).*

1.19.3 .20 Disadvantages:

The four-plate test it's not enough sensitive to all antibiotics e.g.: Sulphonamide and chloramphenicol, to ensure that they are under the MRL values, the test is incapable to determining which antibiotic of a certain class is present and false positive and negative results have been reported (Okerman *et al.*,1998).

1.19.3 .21 Premi Test:

The Premi Test used to be essentially performed according to the manufacturer's instructions.

The check is based on the analysis of 100 µl of liquid sample extracted from the tissue. For the preparation of kidney juice, a10 ml centrifuge tube was filled with roughly cut pieces of kidney taken from the cortex-medulla interface. This sample used to be heated for 10 min. at 80ºC, then cooled down and centrifuged for 10 min at 27000 x g.

Sample preparation for muscle was performed in a similar way. Samples of 100 µl of supernatant were applied on the test vials and removed after 20-30 minutes of pre-incubation at room temperature.

The vials were sealed and transferred to a 64ºC water bath and incubated until most of the samples had become yellow, which was usually after approximately 3 hrs with muscle fluid and 4 hrs when kidney used to be analyzed.

Samples showing a positive result, which used to be described as the absence of any color change, have been retested the next day, which includes a penicillinase test for identification of beta-lactam antibiotics. Only samples positive in this 2nd test have been forwarded for chemical confirmation. (Fac, 2010).

1.19.3 .22 Disadvantages:

With respect to tetracyclines, it has been shown that Premi Test lacks enough sensitivity to detect these antibiotics at the MRL in muscle (Okerman *et al*., 2004; Pikkemaat *et al*., 2009a).

1.19.3 .23 The Nouws Antibiotic Test (NAT):

The Nouws Antibiotic Test (NAT) is the routine antibiotic screening method applied to199 slaughter animals in the Netherlands (Fac, 2010) comprises a 5-plate (residue group-specific) initial screening based on the analysis of renal pelvis-fluid (Pikkemaat *et al*., 2008), and two subsequent post-screening tests for further analysis of kidney and/or muscle of suspect animals (Pikkemaat *et al*., 2009a; Pikkemaat *et al*., 2009b). The EU4pt, the NAT and the Premi Test (muscle and kidney), had been performed in parallel on slaughter animals tested within the framework of the national monitoring program.

1.19.3 .24 1Method:

The Nouws Antibiotic Test is a test system involving a preliminary screening of renal pelvis fluid (pre-urine) and post-screening of muscle and kidney. Initial and post-screening tests each comprise a series of test plates, every optimized for the

detection of one or two antibiotic groups in a particular matrix. The initial screening comprises 5 plates: a *Bacillus cereus* ATCC 1178 plate specific for tetracyclines (T), a *Kocuria rhizophila* ATCC 9341 plate specific for beta-lactam antibiotics and macrolides (BandM), a *Yersinia ruckeri* NCIM 13282 plate specific for quinolones (Q), a *Bacillus pumilus* CN 607 plate specific for sulfonamides and diaminopyrimidines (S) and a *Bacillus subtilis* BGA plate particular for aminoglycosides (A). The exact composition of the individual test plates and the procedure had been described in detail in (Pikkemaat *et al*., 2008). In brief, an incision is made in the kidney and renal pelvis is collected by means of absorption to paper disks, which are placed on the interface of the medulla and the cortex. Each kidney is sampled with five paper disks, one for each test-plate. The paper disks are applied to punch holes in the test plate and supplemented with a plate particular buffer. After overnight incubation, the emergence of a growth inhibition area indicates the presence of antimicrobial residues in the animal.

Suspect samples, showing an inhibition zone on one or more test plates, are additionally analyzed by post-screening of kidney and/or muscle, limited to the residue group for two which the initial screening tested positive. Samples for post-screening are prepared by homogenizing kidney or muscle and isolating tissue fluid from the homogenate by centrifugation after a brief heating step. The post-screening is based on a multi-plate principle similar to the initial screening and described in detail in Pikkemaat *et al*. (2009b) for kidney and in Pikkemaat *et al*. (2009a) for muscle.

1.19.4 Immunoassays:

These methods are primarily based on the interaction antigen-antibody which is very specific for a residue. The most common technique is the enzyme-linked immunosorbent assay (ELISA).

ELISA kits are available for a specific residue such as sulfamethazine or a group of related compounds such as sulphonamides. ELISA kits have proven accurate overall performance for the analysis of antibiotic residues in meat (De Wasch *et al*.,2001; Lee *et al*., 2001; Gaudin *et al*., 2003; Cooper *et al*., 2004; Huet *et al*., 2005; Wang *et al*., 2006; Mahgoub *et al*., 2006; Kadim *et al*., 2009), and especially in the analysis of antibiotic residues in meat like tylosin and tetracycline, (Zuo and Ye, 2006).

There are different formats for antigen quantification like the double antibody or sandwich ELISA tests and direct competitive ELISA tests.

Radioimmunoassay is based on the measurement of the radioactivity of the immunological complex (Samarajeewa *et al*.,1991).

The assays based totally on immune or receptor affinity are designed to give a positive response in line with the level of interest in the matrix tested. They are used each day for self-control in the milk industry to screen residue of several antimicrobial residues such as ß-lactams, Sulphonamides, and tetracyclines (Navratilova, 2008). Effective kits are developed for some aminoglycosides and are used to screen these compounds in kidney or urine by some countries. Some laboratories use them also as publish screening test after a positive inhibitory test to provide data about the chemical family of the residue. ELISA tests for analysis of ß-lactams, chloramphenicol, tylosin, tetracyclines, nitroimidazoles, sulphonamides and also sedatives had been reported (Sai *et al*., 2010; Fernández *et al*., 2010 Babington *et al*., 2012).

1.19.5 Advantages:

An important benefit of immunoassays is that they are able to observe the presence of antibiotics at very low levels, which makes them even useful for screening of

banned substances. The kits allow the analysis of a large range of samples per kit, do not require sophisticated instrumentation, the results are available in a few hours and are quite specific and sensitive (Shankar *et al*., 2010).

ELISA it's a confirmatory test in accordance to Tajik *et al*. (1998) the confirmatory methods using more complex and advanced techniques such as ELISA and HPLC.

1.19.6 Disadvantages:

However, the main challenge of immunoassays is the manufacturing and supply of antibodies that should be selective about the targeted antibiotic compound or group (Shankar *et al*., 2010).

1.19.7 Biosensor

Biosensors are designed to operate in actual time and be able for the simultaneous detection of single or multiple veterinary drugs residues in a sample at a time (Elliott *et al*.,1998). In general, these new technologies are getting good reception in control laboratories due to the reduction in total time and the possibility to analyze simultaneously multiple residues in short time for many samples (Franek and Hruska, 2005).

biosensors are designed against precise classes of antibiotics and, in fact, have shown good detection of tetracycline, streptogramin and macrolide antibiotics in milk and serum. The design of these sensors is compatible with the ELISA-type format and the loss of color gives a readout that is proportional to the antibiotic concentration (Weber *et al*., 2004). Different kinds of biosensors have been developed to screen veterinary drugs (Berendsen, 2013). They utilize biological molecules, such as enzymes, or antibodies, capable of recognizing specifically

targetted analytes. The molecules are coupled to a transducer that responds to the reaction between the analyte and the bound biological molecule. The resulting biochemical signal is measured optically or converted into the electronic signal that is further processed inappropriate equipment. Some authors have reported that there is no need for sample clean-up (Shankar *et al*., 2010).

The reporter gene assays biosensors consist of a genetically modified bacterium, containing an inducible promoter, responsive to a antibiotic, coupled to a reporter gene or operon (Bovee and Pikkemaat, 2009). Based on the presence or absence of responsive antibiotics, the reporter gene induces a fluorescent sign, or the operon impacts the transcription to produce or inhibit a signaling process (Berendsen, 2013).

The tetracycline cell-biosensor used to be found to be more sensitive and faster compared with the microbial inhibition test (Pikkemaat *et al*., 2010).

1.19.6 .8 The important advantages (Toldra and Reig, 2006).

1- Biosensor is easy to use

2- Availability of results in a short time,

3-Analysis of multiples residues in one shot, full automatization,

4- High productivity (high throughput technique of up to 120 samples per hour).

1.19.6 .9 Disadvantages

1- The technique includes high operative costs

2-The analysis is restricted to available chips

(Toldra and Reig, 2006).

1.19.7 Chemical methods:

Among chemical methods are high-performance liquid chromatography (HPLC), gas-liquid chromatography, radioimmunoassay, thin layer chromatography (TLC) and electrophoresis (Ramirez *et al*., 2003).

1.19.7 .1 Thin layer chromatography:

TLC methods are also employed for antibiotic screening, as they can provide high sample throughput and especially high detection sensitivities. Silica and cellulose acetate plates are typically employed, and a variety of solvents and mixtures of solvents used for analyte separation (Shankar *et al*., 2010).

TLC-bioautography is a popular method for the analysis of antibiotic residues. Following separation by TLC, the analytes are detected by means of a microbial inhibition assay. The chromatography plate may also be incubated against an agar plate seeded with sensitive micro-organisms (Choma *et al*., 2002). TLC has been applied to a large vary of antibiotic residues including sulphonamides, aminoglycosides, macrolides, ß-lactams (McGrane,2000), clenbuterol, nitroimidazole, other agonist and thyrostatic drugs (Shankar *et al*., 2010). TLC-mass spectrometry has been reported as antibiotic residue screening method two Various detection techniques have been employed. Detection may additionally require the addition of a visualization agent, such as Fast Violet B salt to the plate, with heating, to create a colored product. Direct UV scanning of the plate is frequently employed. Derivatisation of the analytes on the plate by fluorescent dyes provides a rapid, less expensive method for detection.

Thin layer chromatography bioautography is a famous technique for the analysis of antibiotic residues. Following separation by means of thin layer chromatography, the analytes are detected via a microbial inhibition assay. The chromatography

plate may be incubated against an agar plate seeded with sensitive micro-organisms (McGrane, 2000).

This approach of screening used to be one of a few screening techniques employed by way of MacNeil *et al*.(1991) for the determination of penicillin residues in veal tissue. The authors reported better sensitivity when penicillin residues have been detected in liver and kidney than similar concentrations in muscle tissue. TLC has been utilized to a massive vary of antibiotic residues including sulphonamides (Gooden *et al*., 1994), aminoglycosides (Medina *et al.,* 1995), macrolides (Petz, 1986), and 3-lactams (Schindler *et al.,* 1986). TLC-mass spectrometry has currently been reported as an antibiotic residue screening method.

The method can be performed manually or with online detection. Manual detection requires removal of the spot from the TLC plate followed via solvent extraction of the analyte, and this solution is subject to MS determination. TLC-MS determination of tetracycline residues has been reported (Oka *et al.*, 1993). The TLC plate was developed using non-volatile solvents (oxalic acid, Na EDTA). (McGrane, 2000)

1.19.7.1.2 Disadvantages of TLC:

1- Needs of sample preparation (extraction, filtration, etc.)

2- High price (only one thin-layer plate per residue searched)

3-Liquid chromatography has been applied successfully for the qualitative and quantitative detection of multi-residues in food samples even though its use has rapidly reduced during the last decade (Toldra and Reig, 2006; Fidel and Milagro, 2006).

1.19.8 The confirmatory test:

Confirmatory methods are techniques that supply full or complementary information enabling the substance to be unequivocally identified and if necessary quantified at the stage of interest. They must be instrumental spectrometric methods and consequently are greater expensive and time-consuming but are supposed to be highly selective to provide unequivocal identification (Berendsen, 2013).

Criteria that define the performance of confirmatory methods for residues have been established. For the application of mass spectrometry in regulatory residue analysis, monitoring of 4 ions is required and ion ratios in samples must be within 20 percent of the ion ratios determined in standards (McGrane, 2000).

1.19.9 High Performance Liquid Chromatography in Residue Analysis

HPLC permits the qualitative and quantitative detection of multi-residues in meat and fish products (Haagsma, 1985; De Bukanski *et al*., 1988; Degroodt *et al*., 1989, 1991; Van Poucke *et al*., 1991; De Brabender *et al*., 1992; Gaugain and Abjean, 1996).

HPLC usage is increasing day by day in the field of residue analysis. The variety of mobile phases, the extensive library of column packings and the variation in modes of operations are the reasons for this technique to be in demand. HPLC has progressed for determination analysis in the food industry after all these benefits combined with various types of detectors available. In residue analysis of edible animal products, the sample often has a lot of higher concentrations of endogenous interfering elements, however, a very low content of residues. It is vital to get admission to the variety of producers for isolations, derivatization, and quantitation

of the compound of interest since the nature and concentration of these components can vary widely (Nollet, 1992).

Typical detections of multi-residues in meat samples are relatively simple and rapid, requiring a preliminary clean-up thru solid-phase extraction followed by using filtration before injection into a reverse-phase HPLC with diode array detection. This procedure has been applied to meat for detection of antibiotics like quinolones (Kirbi *et al*., 2005), sulphonamides, b-lactams and macrolides and tetracyclines, veterinary drugs (Reig *et al*., 2005a), anabolic steroids and corticosteroids like dexamethasone (Reig *et al*., 2006).

In some cases, the compounds can be further identified thru diode array or fluorescence detection. Ten quinolone residues (ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, flumequine, marbofloxacin, nalidixic acid, norfloxacin, oxolinic acid, sarafloxacin) in meat have been screened and spectrometry (Thevis *et al*., 2003) or liquid chromatography-mass spectrometry with atmospheric pressure chemical ionization (APCI). ESI ionization technique facilitates the analysis of small to relatively large and hydrophobic to hydrophilic molecules and is thus very adequate for the evaluation of veterinary drug residues even though it is more sensible to matrix effects than APCI ionization (Dams *et al*., 2003). ESI and APCI interfaces are the sources of preference to promote the ionization of antibiotics and both confirmed with HPLC and fluorescence detection. Manipulation and the relatively short time needed per sample. Recent developments in new systems and columns that allow high speed and decreased analysis time are being already commercialized and will contribute its extended use. It ought to be taken into account that sample extraction and clean-up are the rate-determining steps in drug analyses. The use of on-line solid-phase extraction

(SPE) with chromatography coupled to mass spectrometry or other spectroscopic techniques are getting widely used in recent years.

They permit for screening with simultaneous confirmation for those suspicious samples. Even although the cost of the instrument is high when a large number of samples are analyzed the costs are reduced and are more competitive. For instance, nineteen veterinary drugs have been reported to be screened in meat by using an extraction cartridge packed with hydrophilic-hydrophobic polymer sorbent followed by means of fast LC using a short C18 column and direct evaluation by way of LC/MS/MS (Tang and Lai, 2006). Other analytical strategies consist in the use of liquid chromatography-tandem mass spectrometry (LC-MS-MS) for the analysis of different groups of substances in meat like corticosteroids (Antignac, *et al*., 2004), b-agonists, chloramphenicol and penicillins, sulphonamides or ionophore coccidiostats in broiler meat (Rokka and Peltonen, 2006).

1.19.9.1The important benefits of HPLC:

According to Toldra and Reig (2006) the essential benefits of HPLC are:

1-It takes a short time (few min/sample) to obtain the results.

2-Has excessive sensitivity and specificity depending on the detector.

3- High automatization leading to high productivity.

4-The possible receipt of more data from spectra when using a diode array detector.

1.19.9.2 The disadvantages: (Toldra and Reig, 2006).

1-Include initial investment (equipment).

2- Need of expertise.

3-Need of sample preparation (extraction and filtration, the addition of internal standard, etc.).

1.19.9.3 **Detection Techniques:**

1.19.9.3**.1UV spectrophotometry:**

The conjugated ring structure of most antibiotic molecules allows detection by UV spectrophotometry. However, for two antibiotic residue analyses, UV detection might also be undesirable, as many materials absorb appreciably in this spectral region, presenting matrix interference problems. Derivatisation methods are frequently employed to enhance detection sensitivity and to overcome the problem of matrix co-extractives, which can mask the presence of the residue. Derivatisation can enable detection at wavelengths beyond that at which most substances absorb or can result in the formation of a molecule with strong absorption properties, producing a high-intensity signal. Alternatively, it can permit a totally new detection method to be employed (McGrane, 2000).

1.19.9.3**.2 Fluorescence detection:**

The addition of a fluorophore, permitting fluorescence detection is frequently employed for antibiotic residue analysis, both in pre-column and post-column mode. Fluorescence detection is more specific and generally offers enhanced detection sensitivity. Pre-column derivatization can affect the separation, both positively or negatively if the moiety added dominates the chromatographic properties. Derivative stability is any other feature to be considered when employing derivatization in the precolumn mode. The number of samples in a run may additionally be limited to the stability time of the derivative. For post-column derivatization, additional tools are required, and extra optimization is indispensable with respect to mobile phase and reagent flow rates, mixing coil length and

diameter. Post-column derivatization can also result in increased baseline noise due to the pumping action of the reagent pump (McGrane, 2000).

1.19.9.3.3 Electrochemical detection:

Electrochemical detection can be employed for antibiotic residues containing amines (penicillins), thiols and hydroxyl groups (aminoglycosides). This non-confirmatory the technique does now not require derivatization but detects analytes directly. Its high sensitivity requires relatively long equilibration times and requires the presence of salts in the mobile phase, to assist ionization of the residue molecules. Oxidation of the analyte, at the surface of an electrode, causes an exchange in current go with the flow and chromatograms are obtained by using plotting current against time. Carbon paste and gold electrodes have been employed for aminoglycoside residue detection (Isoherranen and Soback,1999). Polarimetric detection has been used for the detection of antibiotic residues that exist as isomers. Specific rotation detection has been applied to the study of erythromycin in milk (Shao *et al*., 1989) permitting identification of various forms of the same drug, which possess minor structural differences. Refractive index detection has also been employed for aminoglycoside residue detection (White and Zarembo, 1981) with a detection limit of 1 mg ml'1. This method of detection is frequently much less sensitive than the more classical detection methods, however, is more specific. Currently, since not all veterinary preparations are required to be chirally pure, the requirement for techniques capable of detecting optically active substances are limited (McGrane, 2000).

1.19.9.3.4 Mass spectrometric detection:

In recent years, a great deal of research has been directed at developing the perfect confirmatory detection technique, and attention has been focused on making MS detection more widely applicable and greater sensitive.

Mass spectrometric detection of antibiotic residues is becoming increasingly popular, as analysts require confirmatory techniques for determining the presence of antibiotic residues. Briefly, mass spectrometric detection involves the ionization of molecules, resulting in a sample of molecular ions and fragments that are unique to that antibiotic.

Mass spectrometric detection can theoretically provide unequivocal identification for all Antibiotics. The excessive price and requirement for skilled operators initially hampered the Application of this approach to veterinary drug residue applications (McGrane, 2000).

1.19.9.3.5 LC-MS:

However, LC-MS is now routinely employed for the determination of antibiotic residues with most MS systems now being commercially available as bench-top LC detectors. The difficulty in obtaining diagnostic molecular ions has led to the existence of a huge range of ionization techniques. Ease of operation and fee have resulted in quadruple instruments becoming most popular. Many LC-MS methods reported in the literature hire thermos pray interfaces.

1.19.9.3**.6 Electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI)** the mass spectrometric analysis of antibiotics has significantly benefited from the development of electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI). The ionization approach employed is

influenced with the aid of a variety of parameters such as mobile phase flow rate and composition, analyte thermal stability, volatility, and ionization state. Criteria that define the overall performance of confirmatory methods for residues have been established. For the application of mass spectrometry in regulatory residue analysis, monitoring of 4 ions is required and ion ratios in samples should be within 20 percent of the ion ratios determined in standards (McGrane, 2000).

1.19.10 Comparison between the tests:

1.19.10.1The One-plate assay used to be particularly similar in sensitivity for detection of P-lactams, sulphonamides, and aminoglycosides to the four-plate test. The One-plate was less sensitive to chloramphenicol and macrolides than the Four-plate test. In general, the One-plate test was once less sensitive for the detection of the tetracyclines and much less sensitive to flumequine yet more sensitive to enrofloxacin (McGrane, 2000).

1.19.10.2 Immunodiagnostic techniques, such as EIA has also featured, offering increased specificity and sensitivity, relative to microbial inhibition methods. In chemical analysis, HPLC remains the technique of choice for antibiotic residues. A wide range of detection techniques is used, including UV, fluorescence and electrochemical detection. The employment of confirmatory detection for routine analysis has increased significantly. The online combination of LC-MS has become a popular technique. The ease of operation and robustness of newly-developed interfaces has resulted in the movements' employment of MS for detection and simultaneous confirmation (McGrane, 2000)

1.19.10.3 Currently, SPE is the sample: Preparation technique most widely employed in antibiotic residue analysis (McGrane, 2000)

1.19.10.4 Microbial inhibition tests:

Generally used for detecting antibiotic residues because they are easy to run and inexpensive. In looking at the improvement of different tests over the years, it is hard to comparatively evaluate them based on published literature on my own because different tissues, tests, and procedures are used. Chemical tests have been viewed too particular and costly for screening but HPLC can detect multiple antibiotics and is fee effective when considering the financial savings of forwarding samples and waiting for results (Pikkemaat *et al*., 2009).

1.20 Residue analysis of live animals:

The difficulties must be considered for residue analysis. In contrast to the difficulties of measuring residues in organs and tissues, most compounds can be easily quantitated from body fluids (blood, plasma, serum, urine, exudates) and only a simple dilution step may also be required before analysis (Bacigalupo *et al*., 1995; Elliot *et al*., 1996; Hagren *et al*., 2005). In humans, plasma, saliva or urine samples are used to monitor drug concentrations in therapeutic treatment or to determine drug abuse. This sampling strategy has been used for many years and is widely accepted as evidence of drug exposure and to estimate concentrations in the body (Dickson *et al*., 1994; Rivier, 2000; Hammet-Stabler *et al*., 2002; Kim *et al*., 2002; Rigamonti *et al*. 2005). For animals, several researchers have proposed the use of body fluids as predictive indicators of the concentration of residues in target tissues that are intrinsically extra challenging to analyze (Ashworth *et al*., 1986; Crooks *et al*., 1998a, b; Peippo *et al*., 2005; Chiesa *et al*., 2006a, 2006b; Heller *et al*., 2006; Haasnoot *et al*., 2007; Schneider *et al*., 2007, 2009; Schneider and Lehotay, 2008). However, the number of researchers in this region is limited. A couple of studies on the disposition of sulfonamides in sheep recognized similarities in the pharmacokinetic patterns of these antibacterials in special tissues and body fluids

(Bevill *et al*., 1977a, 1977b). Subsequently, Ashworth and colleagues (1986) evaluated the use of blood samples as a means for pig producers to detect animals with feasible violative or unlawful residue concentrations of sulfamethazine before delivery the animals for slaughter. They reported that the concentration of residues in liver (the target tissue) would exceed the tolerance restrict when the concentration in blood exceeded the 45ppb (Ashworth *et al*., 1986). In cattle, the different research explored the use of blood as a predictor of the concentration of antibacterial residues as a pre-slaughter test (Chiesa *et al*., 2006a, 2006b). According to (Chiesa *et al*., 2006b), the researchers additionally measured the concentration of residues in urine and mentioned that this measurement was highly variable depending on factors such as the time stored in the bladder and pH of the urine.

In poultry, only one study has examined the blood: tissue relationship of antibacterial residues. Haasnoot and co-workers (2007) evaluated the use of body fluids as markers for the presence of different sulfonamides in distinctive edible tissues (skin and fat, liver, muscle) of broiler chickens. These researchers reported that the blood: tissue ratio varied significantly depending on the tissue, with higher concentrations in blood and blood: tissue ratios of 6.2:1 in muscle. To evaluate the utility of using blood to screen for residues in muscle, we performed research to determine the pharmacokinetic relationship between blood and muscle for two different antibacterials (enrofloxacin and oxytetracycline) in market aged broiler chickens.

CHAPTER TWO

MATERIALS AND METHODS

2.1 Study Area

This study was carried out in Khartoum State; is the national capital and the largest city of Sudan it's located at the confluence of the White Nile and the Blue Nile the two Niles unite to form the river Nile. The state lies between longitudes 31.5 to 34 E and the latitude 15 to 16 N. Sudan. Samples examined for detecting antibiotics residues were collected from Almoileh and Albarakah slaughterhouse, which distributes meat to most of the main meat markets.

2.2 Collection of samples

The target samples were 75 samples from Bovine **(28)**, Ovine **(28)**, Caprine **(8)** and processed meat **(11)** from local market. The samples were kidneys, livers and muscles, in addition to bovine lungs and heart.

All samples collected in plastic bags and all of them were put in icebox to be delivered into deep freezer for further laboratory analysis.

2.3 Questionnaire survey

The questionnaire was designed to have basic information about the manner of using antibiotics in Khartoum State and the questionnaire was collected from 25 veterinarians where selected randomly that means not all the veterinarians have the same chance for being selected and this was called Non-probability sampling methods as described by Thrusfield (2007).

2.4 One plate test (O. P. T.)

One plate test (O. P. T) was used as described by Koenen -Dierick *et al*. (1995) and Nada (1996). The test organism was *Bacillus subtilis* (strain ATCC6633). The test

depends on bacterial growth inhibition. Inhibition zone appears around the filter paper that contained tissue fluid of samples. The sample was considered positive when the inhibition zone was 2 mm and more, doubtful when it was 1 to 2 mm, and negative when it was less than 1 mm.

2.4.1 The principle of method:

The principle of the test is preparing plates seeded with sensitive bacteria (*Bacillus Subtilis*) at specific conditions that can presumptively indicate the presence of specific antimicrobial group residues. The samples can be applied on top of the agar layer. After over-night incubation, the presence of an antimicrobial residue becomes visible as an inhibition zone around the sample. The size of the inhibition zone depends on the type of residue and its concentration, while the sensitivity of the test is affected by many factors, such as indicator organism, pH, type of growth medium, and thickness of the agar layer (Bovee and Pikkemaat, 2009).

2.4.2 Test organism

B. subtilis (strain ATCC6633) was used.

2.4.3 Sterilization

2.4.3.1 Hot air oven

This method was used for sterilization of clean glass containers, which were wrapped in paper or put in stainless steel cans, temperature was 160°C for one hour (Stainer *et al*., 1986).

2.4.3.2 Red heat

This method was used for sterilizing wire loops, straight wire and tissue forceps (Cruick- Shank *et al*., 1975).

2.4.3.3 Autoclaving

This method was used for sterilization of culture media and for materials that could not stand the dry heat. The temperature was 115 to 121°C under 10 to 15-pound pressure for 15 to 20 min (Barrow and Feltham, 1993).

2.4.4 Samples handling:

An incision was made into the liver sample to have around 0.5 gram in 5 mm thick to be placed immediately into the Petri dish.

2.4.5 Nutrient agar preparation

Twenty-eight grams of nutrient agar powder (Oxoid, 2006) was placed in 1000 ml of distilled water. The medium was autoclaved at 121°C for 15 min. The medium was cooled at 50°C. Twenty milliliters of the medium was distributed for each Petri dish and the solidified agar was kept in refrigerator at 4°C.

2.4.5.1 Preparation of standard test organism culture

B. subtilis was seeded in nutrient broth. Sporulation culture medium was perpetrated in 500 ml flat slide bottles loosely closed with screw caps for adequate aeration. Each bottle contained nutrient broth culture of *B. subtilis* and incubated at 37°C for 48 h until 90% of culture was spores.

2.4.5.2 Test procedures

One milliliters of standard organism were added to 20 ml of nutrient agar in each Petri dish, then mixed and left for 10 min to solidify on a level surface bench and with clean dry and sterile forceps were picked up filter paper and tested. Plates were incubated at 37°C until growth was visible within 24 h. Zone inhibition was observed around the samples when the sample containing antibiotic was measured

in millimeters by the ruler. Negative samples did not show such clear zone (Negative = less than 1 mm). Interpretation of the results was done as mentioned earlier (Nada, 1996).

2.4.5.3 Cultivation media and solutions:

To prepare test plates with *B. subtilis*, test agar pH 6 was used. Further, sporulation medium was used (containing, in 500 ml, proteose peptone 1.725 g (HiMedia), casein enzyme hydrolysate1.725 g (HiMedia), NaCl 2.55 g; Agar No. 1 6.5 g (Oxoid,2006); potassium dihydrogen phosphate 0.5 g (KH2PO4, Merck, Darmstadt, Germany) pH 7, sterilized at 121 °C for 15 min.

2.4.5.4 Preparation of *B. subtilis* spore suspension:

The suspension was prepared in accordance with the method of Bogaerts and Wolf, (1980).

2.4.5.5 Preparation of test plates with *B. subtilis* CCM 4062:

The pH 6 test agar was heated to 55 °C and inoculated with *B. subtilis* spore suspension to approximately 104 CFU·ml-1. The agar with the test strain was pipetted at 4 ml doses to pre-heated sterile glass Petri dishes of 90 mm in diameter.

2.4.5.6 Preparation of samples:

Samples were removed from the deep-freeze and allowed to reach a temperature of about - 5 'C, before the outer (contaminated) surface was removed with a sterile scalpel. A cylindrical piece from the target organ was removed from each sample using a sterile corn borer (8 mm internal diameter), 2 mm thick, were cut from it. The *B. subtilis* plates were incubated at 30 'C for 18-24 h. A positive test result was recorded when inhibition zone not less than 1-2 mm across.

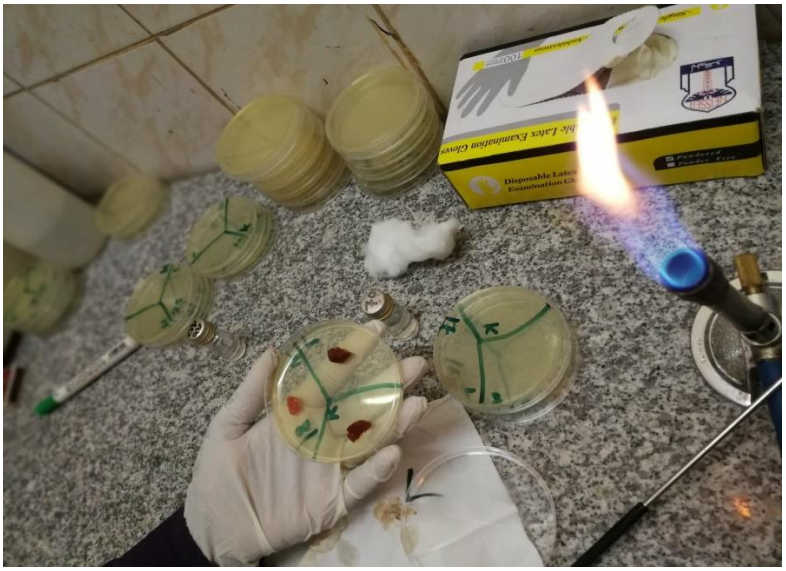

Figure (1): Fixing the samples

Figure (2): clear inhibition zone

2.5 Secondary data:

Secondary data are derived from existing information sources such as references, textbooks, journals, reports, evaluation studies etc.

2.6 Data analysis:

The data were analyzed by using IPM SPSS (Statistical Package for Social Science) version 24 and the statistical methods used in the study are:

1. Cranach's alpha
2. Frequency
3. Percentage
4. Graphic formats

CHAPTER THREE

RESULTS

3.1 Bacterial Screening Test Result

In table 1 the results showed that the positive samples for the present of antibiotics residues Bovine, Caprine, Ovine and processed meat were 46.4%, 12.5%, 96.4% and 27.3% respectively. While the negative samples were 53.6%, 87.5%, 3.6% and 72.7% respectively.

Inhibition zone	Bovine %)	Caprine %)	Ovine (%)	Processed meat (%)	Total (%)
Absent	15 (53.6)	7 (87.5)	1 (3.6)	8 (72.7)	31 (41.3)
Present	13 (46.4)	1 (12.5)	27 (96.4)	3 (27.3)	44 (58.7)
Total	28 (100)	8(100)	28(100)	11(100)	75(100)

Table 1: presence of inhibition zone in meat (n=75) of bovine, caprine, ovine and processed meat in Khartoum state

According to table 2 the percentage organs tested from kidney, liver, heart, muscle and lung were 85.3%, 85.3%, 48%, 100% and 48% respectively.

Kind	Organ tested (%)	Missing (%)
Kidney	64 (85.3)	11 (14.7)
Liver	64 (85.3)	11 (14.7)
Heart	36 (48)	39 (52)
Muscle	75 (100)	0
Lung	36 (48)	39 (52)

Table 2: percentage of tested organs antibiotics residues in Khartoum State

In figure 1: Inhibition zone for Bovine the result revealed that the inhibition zone for Bovine, >2 mm for kidney, liver, lung, heart and muscle was 1-2-1-0 and 0 but the 1-2 mm was 6-4-4-5.

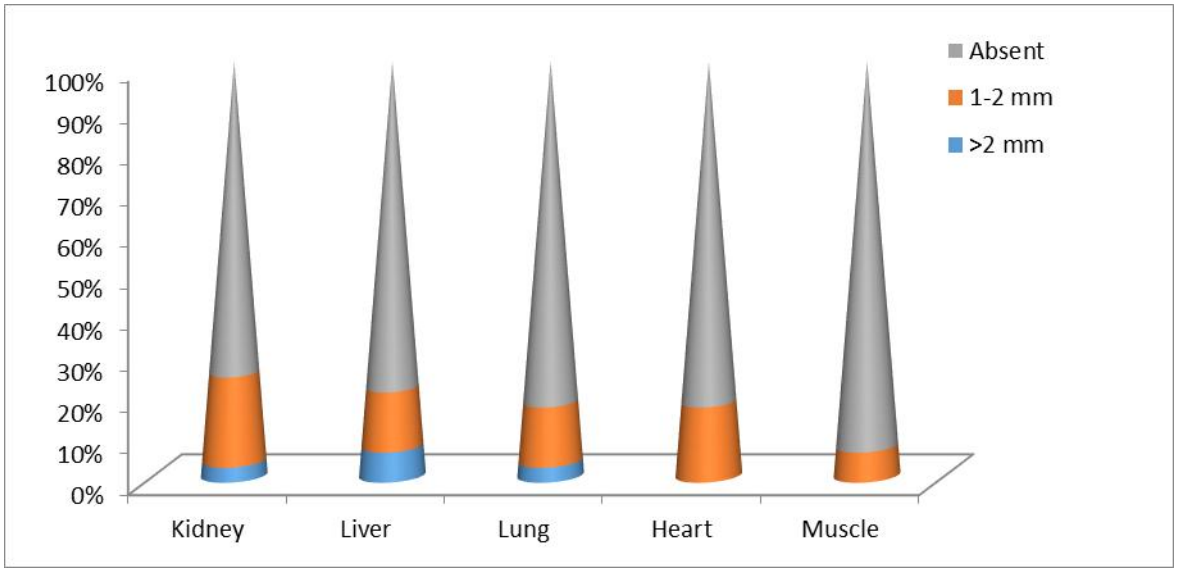

Figure 3: Inhibition zone for Bovine

Showed the inhibition zone for ovine (>2 mm) for liver, kidney and muscle was, 15, 6 and 12, but the inhibition zone (1-2 mm) 6-15 and 8.

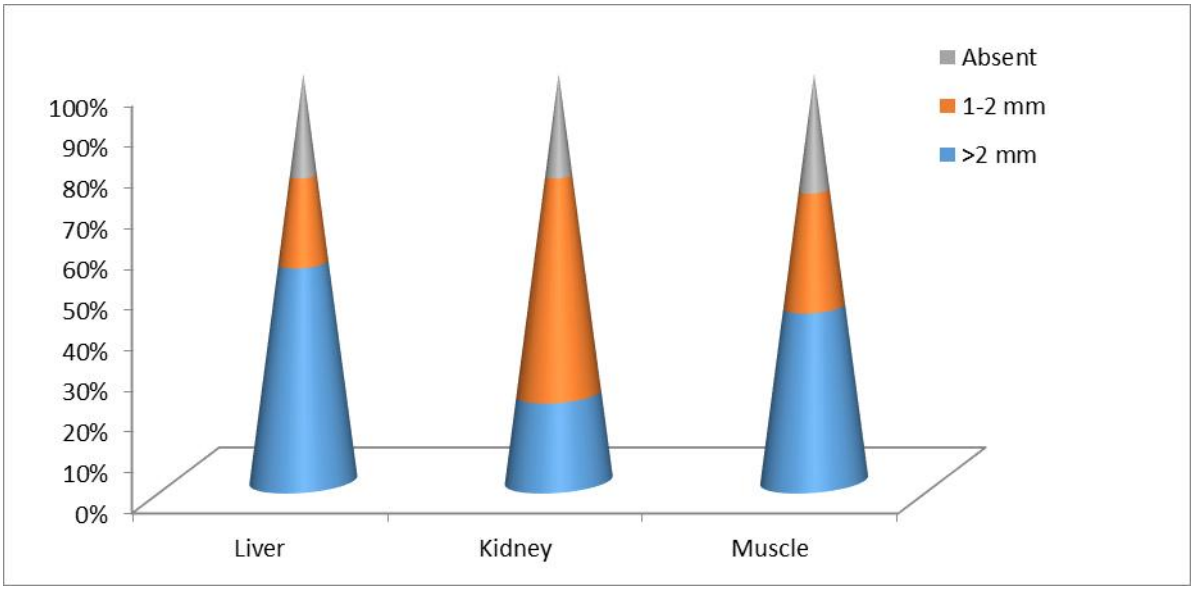

Figure 4: Inhibition Zone of ovine meat (n=28) in Khartoum state

In figure 4: the result explained that the caprine inhibition zone (>2 mm), for liver, kidney and muscle was 0-1-0 and for (1-2 mm), 1-0-0.

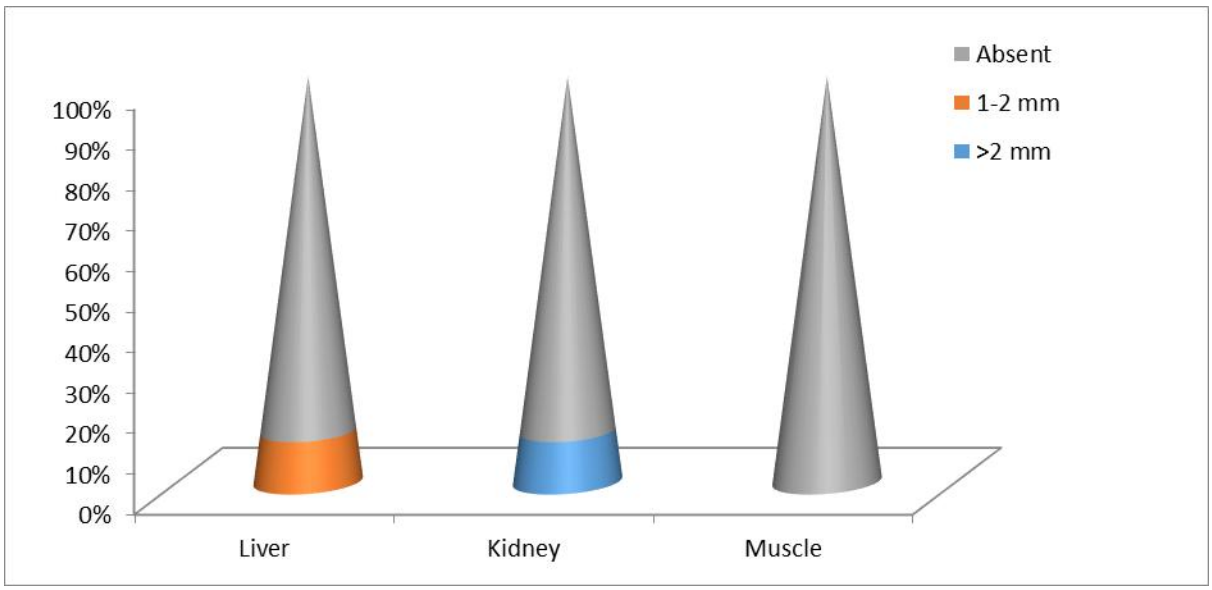

Figure (5): Inhibition Zone for Caprine meat (n=8) in Khartoum State

Processed meat the distribution was 27.3% positive and 72.7 negative (figure 5)

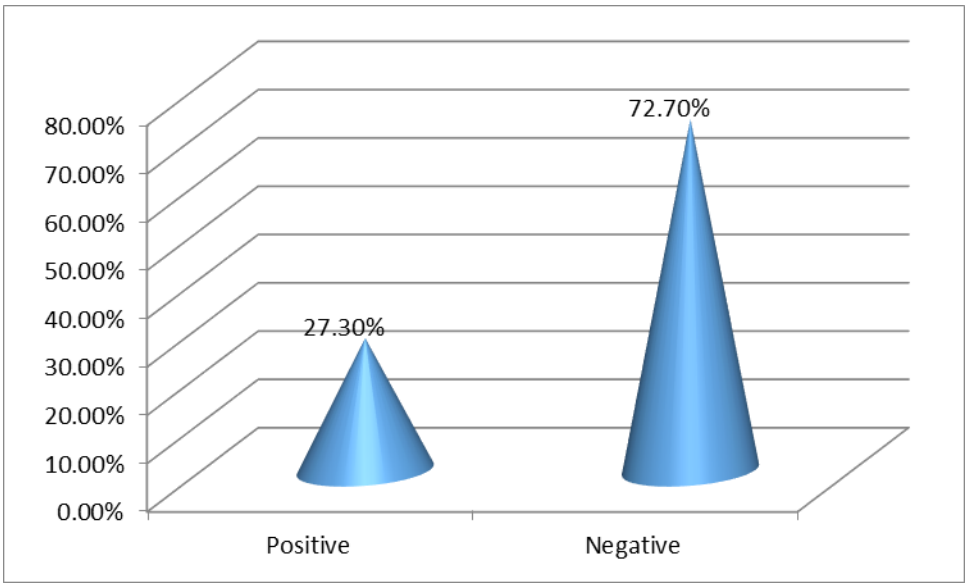

Figure (6): Processed Meat (n=11) in Khartoum State

3.2The Questionnaire Results:

About 60.0 % of the veterinarians were given the owner information about withdrawal period, but 40.0 % of them were sometimes given it.

No.	Items	Yes	No	Sometimes
1	Do you give owners ATIPS about the withdrawal period	15	10	0
		60.0	40.0	0.0
2	Do the owners comply with guidance	5	6	14
		20.0	24.0	56.0
3	Do you adhere to the dosage mentioned in the prescription	6	15	4
		24.0	60.0	16.0

Table 3: Answers of the respondents (n=25) for withdrawal period in Khartoum State

Figure 7: showed the views of the distribution of the sample about 84.0% of the veterinarians they don't know what is suitable confirmatory or screening test for drug residues in Khartoum State

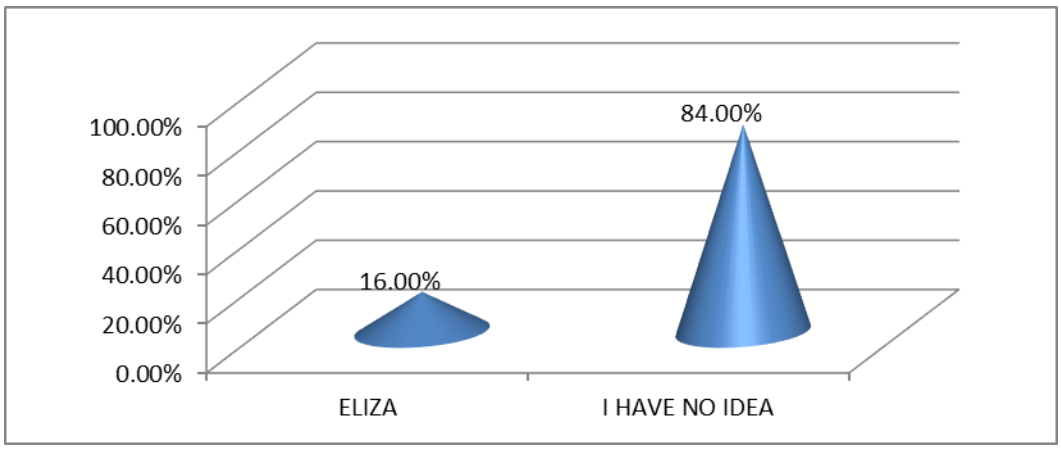

Diagram (7) the distribution of the sample by the ELIZA

In table no (4): **The most antibiotic/s used in your work**? the oxytetracycline is higher (%72.0) and aminoglycoside (%4.0) and I have no idea (%0.0). **The most antibiotic/s used for the treatment of calves, lambs and poultry in your work**? quinolones were (%32.0) and sulphonamide were (%24.0) and I have no idea by (%0.0).

The harmful antibiotics for animal's health? chloramphenicol were (%48.0) and the sulphonamide (%24.0), aminoglycoside (%16.0) quinolones (%8.0) and I have no idea (%4.0).

The harmful antibiotics residuce for human health: the chloramphenicol was (%44.0) and I have no idea by (%12.0).

No	**Items**	Oxytetracycline	Sulphonamide	Quinolones	Chloramphenicol	Aminoglicoside	I have no idea
1	What is the most antibiotic/s used in your work	18	2	2	2	1	0
		72.0	8.0	8.0	8.0	4.0	0.0
2	What is the most antibiotic/s used for the treatment of calves ,lambs and poultry in your work	3	6	8	3	0	0
		12.0	24.0	32.0	12.0	0.0	0.0
3	From your knowledge ,what is the harmful	0	6	2	12	4	1
		0.0	24.0	8.0	48.0	16.0	4.0

	antibiotics for animals health						
4	From your knowledge ,what is the harmful antibiotics residuce for human health	5	1	5	11	0	3
		20.0	4.0	20.0	44.0	0.0	12.0

Table 4: the frequency and percentage of the antibiotics uses and the harmful effect on human and animal's health

The results of table (6) Interpreted as follows:

The value of chi – square calculated to signify the differences in all the table no (6) the values were P-value (0.000) is lower than the level of significant value (5%) and there is no significant and this is refer to the existence of differences statistically.

No	Phrases	Chi-square value	df	Sig.	Median	Interpretation
1	what is the most antibiotic/s used in your work	15.24	5	0.00	1	Oxytetracycl Ine
2	what is the most antibiotic/s used for the treatment of calves ,lambs and poultry in your work	15.20	3	0.00	3	Quinolones
3	from your knowledge ,what is harmful antibiotics for animals health	16.20	5	0.00	4	Chloram phenicol
4	from your knowledge ,what is the harmful antibiotics residuce for human health	19.82	5	0.00	4	Chloram phenicol

Table (5) illustrates chi-square test results for the Antibiotics

In Figure 7: the views of the distribution of the sample for the antibiotics injection follow-up (%8.0) they are answer Yes, I'm and (%92.0) of the owners/workers follow-up the treatment by their selves.

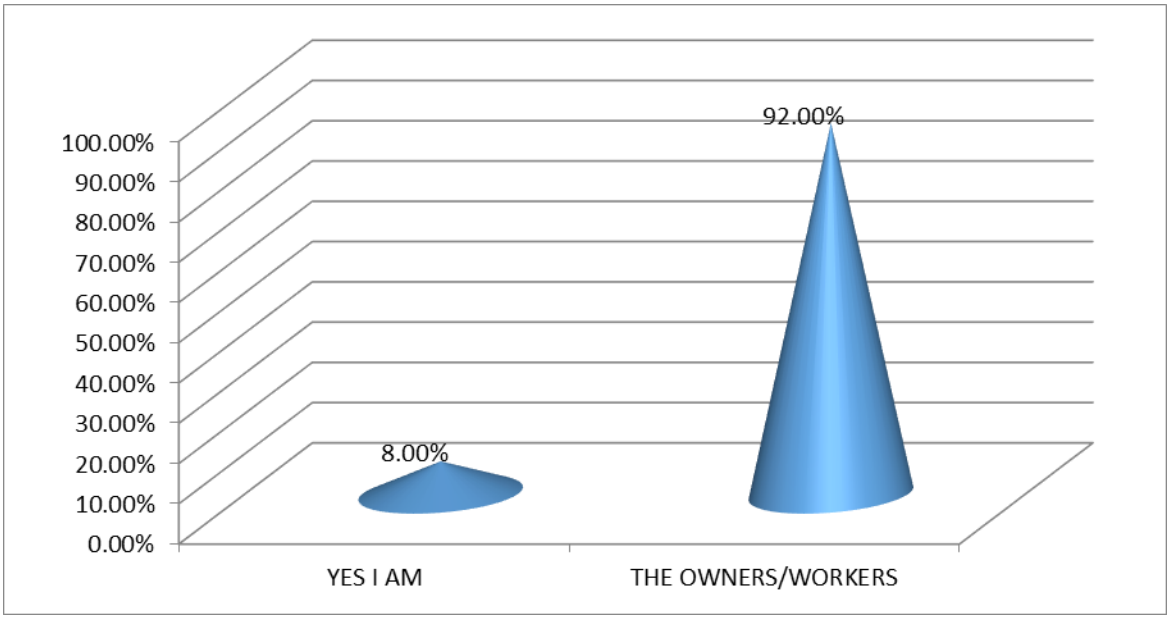

Diagram (8): Follow-up of antibiotics administration

Table 7: do you treat the sick animals with your - self or the owners / workers follow the antibiotics course?

There is no significance value of chi – square calculated to signify the differences between the results (17.64) with P-value (0.000) which is lower than the level of significant value (5%) These refer to the existence of differences statistically.

No	Chi-square value	df	Sig.	Median	Interpretation
25	17.64	1	0.00	2.0	**the owners/workers**

Table (6): Follow-up of antibiotics administration

The views of the distribution of the sample by the yes (%12.0) and no by (%88.0) and sometime by (%0.0) and I have no idea (%0.0) for the using of drug residuce testing after slaughtering.

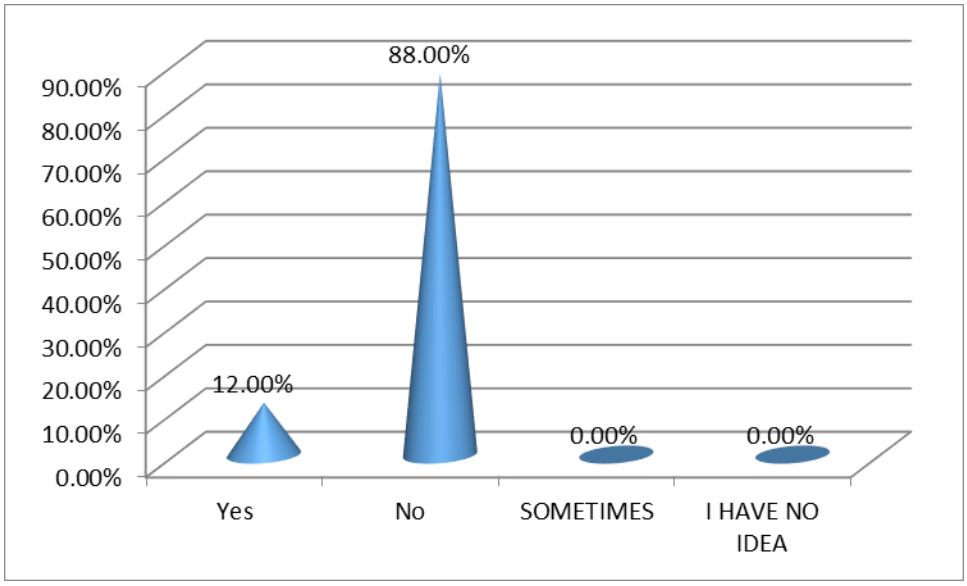

Figure 9: check the antibiotics residues after slaughtering

In figure 9: the views of the distribution of the sample by the yes (%72.0) and **I have no idea by** (%12.0) for the antibiotics banned globally.

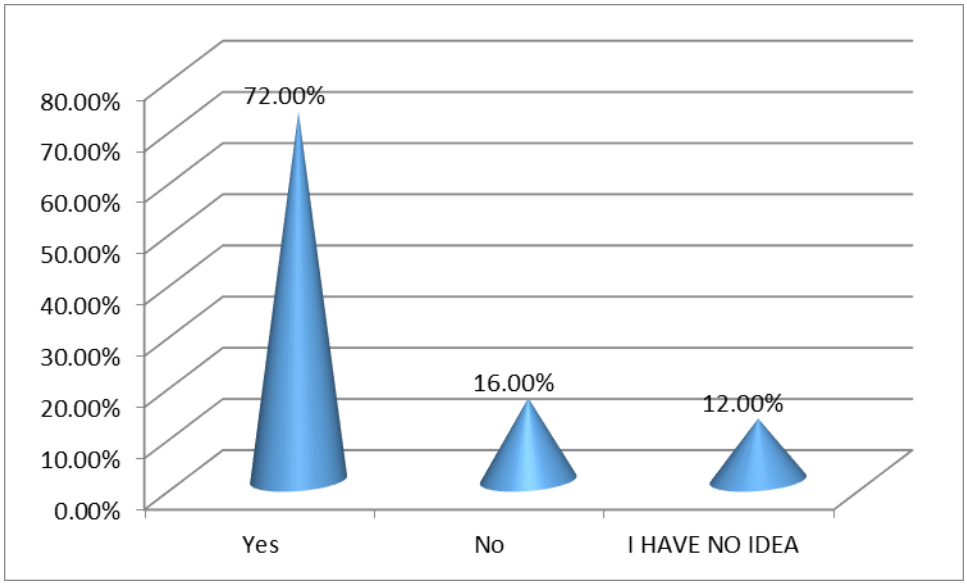

Figure (9) are there antibiotics that have been banned globally

Table 7: there is an antibiotic that have been banned globally:

The result were (41.25) with p-value (0.000) which is lower than the level of significant value (5%) These refer to the existence of differences statistically.

Table 7: are there antibiotics that have been banned globally

No	Chi-square value	df	Sig.	Median	Interpretation
25	41.25	2	0.00	3.0	Yes

Figure 10: there was a question do you think there is testing to check antibiotic residues before slaughtering

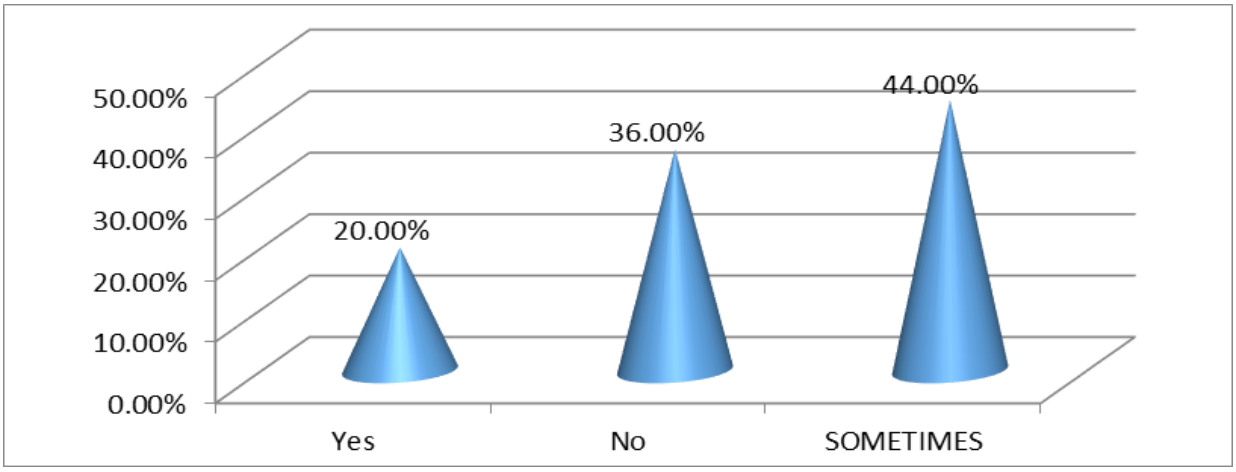

Figure 10: views of the distribution of the age sample by the yes (%20.0) and no by (%36.0) and sometime by (%44.0).

The distribution of the sample by the yes (%0.0) and no by (%96.0) and sometime by (%4.0) diagram (11).

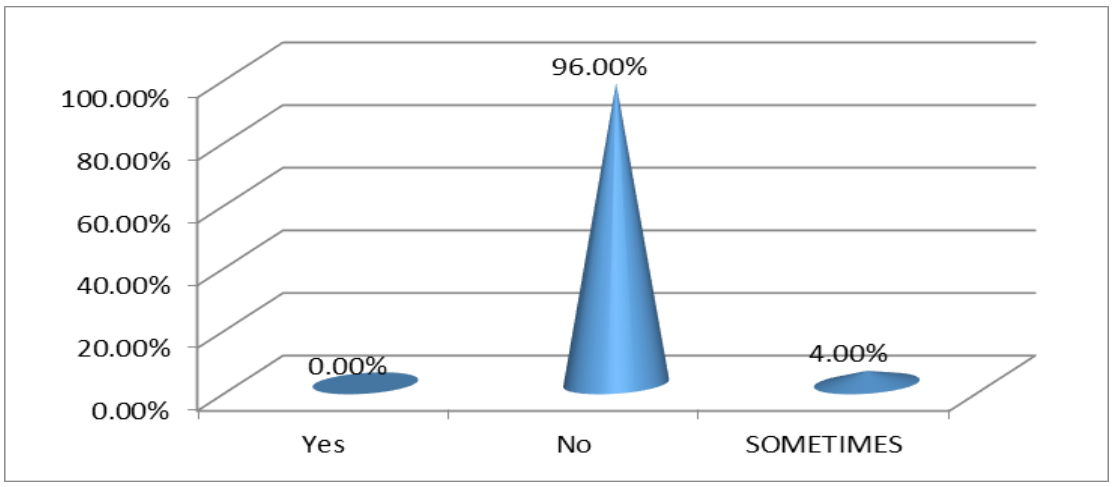

Diagram (11) Do you check the antibiotics residues before slaughter

CHAPTER FOUR

DISSCUSSION

4.1 Bacterial Screening Test:

In the present study the antibiotic residues were measured in meat of bovine, caprine, ovine and processed meat (Table 1, 2). This results in agreement with Mohamed *et al*. (2011) and Hala (2006).

Our results disagreed with Alla *et al*. (2011) in Sudan and he reported that only 3% of beef muscles contained antibiotic residue.

Masztis (1984) who found (0%) and Shahid *et al*., (2007) who is checked up (33 livers, 33 kidneys and 34 muscles) from local market in Rawalpindi and Islamabad the result were positive for antibiotic residues is (39.4%), (27.3%) (20.6%).

In a related study using samples obtained from open markets in Sokoto, Nigeria, 44% of slaughtered cattle were found to contain residues of antibiotics (Ibrahim *et al*., 2009), residues have been reported in 21% of meat samples in Ghana (Novais *et al*., 2010), and 70% in Tanzania (Kurwijila *et al*., 2006).

Tajick and Shohreh (2006) also found that more than 50% of poultry meat tissues tested in Iran had residues of antimicrobials.

Results of microbiological screening were similar to findings in the screening of broiler meat and beef sold in the markets of Ankara, turkey by Er *et al*., (2013) who discovered that 45.75% of chicken and 57.7% of beef were positive for quinolone residues.

The presence of antibiotic residues in meat is a serious problem that is yet to be addressed in developing countries like Ghana where safety of food regarding drug residue is highly questionable. The antibiotic residues detected in meat (liver, fat and kidney) from slaughtered cattle intended for sale to the human populace in Kumasi could be attributed to irrational use of drugs in food animal ‘s consequent to lack of regulatory system for veterinary drug use and control as observed previously (Aliu, 2004). In addition, stakeholders involved do not adhere to withdrawal period. Non-adherence to withdrawal periods is the major cause of chemical residues (Riviere and Sundlof, 2001).

In figure (2), the obtained result for the inhibition zone in bovine, >2 mm for kidney, liver, lung, heart and muscle was resembled to the study of Alla *et al*. (2011) who detected the presence of antibiotics residues in Ghanawa slaughterhouse, Khartoum State using one plate test (O. P. T.). The test organism was *Bacillus subtilis* (strain ATCC6633). The sample was considered positive when the inhibition zone was 2 mm and more, doubtful when it was 1 to 2 mm and negative when it was less than 1 mm. Out of 300 animals (17.33%) showed positive results in one or more of their organs. Out of 300 kidneys tested, (10%) showed positive result, while out of 300 livers tested, (7.66%) were positive, and out of 300 muscles tested (3%) were positive.

In figure (3) the inhibition zone for ovine (>2 mm) for liver, kidney and muscle was, 15, 6 and 12, but the inhibition zone (1-2 mm) 6-15 and 8. 25 % of the sheep liver samples were positive to antibiotics while 75% was negative. Relationship between the percentage of positive inhibition zone (IZ) higher than 2mm or less than 2 mm and negative IZ < 2 mm the analysis concentration was calculated, from which the calculations were made of the concentration threshold value at which the tests become unreliable and, at the same time, a concentration to which the given

strain is sensitive. When evaluating results in individual Petri dishes, they measured the diameter of the inhibition zone (IZ) of all samples there, and then they determined the mean diameter of IZ in mm. A sample was considered as positive when the mean diameter of IZ thus calculated was ≥ 2 mm. The method's sensitivity to an antimicrobial substance was defined as the lowest concentration at which a positive result was obtained. However, in the research, a method was considered as sufficiently sensitive at a given antibiotic concentration when a positive result, i.e. IZ ≥ 2 mm, was obtained with all the samples (Pavlina *et al*., 2010). This result is closed to the study conducted with Hind *et al*. (2014), they found a total of 221poultry tissue samples screened for antibiotic residues were 27% of the samples tested positive residues and 73% were negative.

Also, this result is like the study of (Shahid *et al*., 2007) done in Pakistan using *B. subtilis* as a test organism, screening of AMR in a total of 100 broiler tissue samples (33 livers, 33 kidneys and 33 muscles) revealed that 13(39.4%) livers, 9(27.3%) kidneys and 7(20.6%) muscles contained antimicrobial residues. Shahid, *et al*. (2007) reported that, the 100 samples processed by STAF test, 29 samples had zone of inhibition ≥2 mm and were considered STAF positive, while 12 showing zone <2 mm were considered STAF negative. The highest number (39.4%) of antibiotic residues was observed in liver samples. While 27.3% kidney samples showed positive results. In case of muscle samples 20.6% were detected as positive. These results agreed well with Jabbar (2004) reported that incidence of antibiotic residues in kidney samples was 70%, in liver it was 60%, while for muscle it was 50%. **The result** explained that the caprine inhibition zone (>2 mm), for liver, kidney and muscle was 0-1-0 and for 1-2 mm, 1-0-0 **(figure 4).**12.5% for the positive sample the result described the low level of the antibiotics uses in caprine when we compare it with ovine and bovine. This result is close to the result

obtained by Ezenduka and Ugwumba (2012), they obtained 10 (25%) of the 40 sampled goats were positive for antimicrobial residues. **In figure no (5)** the views of the distribution of the sample by positive was %27.3 and negative was %72.7 for the processing meat.

There were related studies by lolo *et al.* (2006) and Javadi *et al* . (2011), the reduction in antimicrobial activity of processed chicken meat was observed to be 28.8%, 66.26%, and 30.9% after boiling, microwaving, and roasting respectively. However, the residues could not be eliminated, and freezing might also act as a factor in reduction of antibiotic residues in frozen samples (Okerman *et al.,* 2007).

In a report, it was found that 90% reduction of the initial level of tetracycline was possible at a continuous treatment of chicken meat for 23.9, 53.2, and 106.6 min by microwaving, boiling, and roasting, respectively (Abou-Raya *et al*., 2013).

In the processed meat of chickens fed with doses of doxycycline. The processes of boiling, microwaving, and roasting were found to reduce the antimicrobial activity by 65, 100, and 25.2%, respectively, indicating a decline in doxycycline residues. However, cooking processes did not eliminate residues from condemned meat samples (Javadi, 2011).

According to, Hussein and Khalil (2013) mentioned studies showed that some of the processing techniques helped to reduce different antibiotics to certain levels. However, this should not be considered as an alternative for the control of antibiotic usage during farming.

4.2 Social aspect discussion:

Owners comply with guidance, withdrawal period and adhere

The questionnaire showed that about 60% of veterinarian did not adhere to the dosage on the prescription (Table 3). These results are nearly the same as the results of Fathalrhman *et al*. (2016) who revealed that 43.3% of the veterinarians at veterinary pharmacies practice whole sale of antibiotics to the dairy farms' owners, 60% guide them to restrict dose, 73.3% advice the owners about the routes of administration. However, only 56.7% from all interviewed veterinarian's advice the dairy farms' owners for withdrawal period.

Alla *et al*. (2011) survey revealed that veterinarian did not restrict to the weight of animal when describing doses which lead to over-dosing or sub-dosing, and there was no following up of cases after leaving the clinic or pharmacy (86%). Furthermore, the veterinarians leave dose restriction and administration to owner (76%). Similarly, Swant *et al*. (2005) found the same results during his survey on antibiotic usage in dairy herds in Pennsylvania. Guiding owners for withdrawal Period? exist (76%).

There was a question to evaluate the awareness about the residue detection technique, 84% of veterinarians they don't know the suitable screening or confirmatory test for residuce only 16% they say the ELISA figure (6), (Nisha, 2008) mentioned the famous confirmatory techniques used for detection and analysis of drug residues same as ELISA, HPLC, liquid chromatography, gas chromatography and paper chromatography.

The results conducted by Nonga *et al*. (2009) indicated that 70% of the farms are positive for antimicrobial residues. Ninety percent of the respondents had knowledge on antimicrobial withdrawal period. However, 95% of farmers slaughtered their chicken before withdrawal period because they were afraid of losses and unaware of the effects of antimicrobial residues in humans. They

suggest that poultry farmers need to be educated on the possible effects associated with use of food with antimicrobial residues.

Usage of Antibiotics groups:

In **Table (5),** and table (6), the **Oxytetracycline** group, represent about 72% of antibiotics groups used for the animals' treatment. This result is close to study conducted by Addisalem and Bayleyegn (2012) and Nonga *et al*. (2013), in Ethiopia and in Tanzania OTC residues in beef samples. Also, this finding agreed with Lynas *et al.*, (1998) in Northern Ireland analyzed feedstuffs, detect the contamination level, **Chlortetracycline** was detected in 50 % of the samples. The results also showed that 32% of **the antibiotics** used in poultry farms lambs and calves. This result was close to study conducted in 2006 in Venezuela wich reported that, of 20 samples, 50% were positive for quinolone residues that exceeded the maximum limit of residues allowed in poultry meat.

Similarly, in 2005, 23% (3 of 13) of fish meat sampled in Chile contained **antibiotic** residues above the established maximum limits. The Iran Veterinary Organization conducted research in Teheran Province by analyzing 270 samples, of which, 24 (8.8%) were positive for **quinolone** residues. In Saudi Arabia, 35% of the samples of broiler meat were positive for quinolone residues. The study explained that **quinolone withdrawal** practices are not being followed properly in the area from which positive samples were obtained Silfrany *et al*.(2013).

There is a study conducted by Hakem (ex Akam, 2013), in which most of positive samples cases were found contaminated by β-lactams and/or tetracyclines (75.81%). In contrast, the macrolides and/or β-lactams and **sulfonamides were** recorded only in 44.35% and 36.29% respectively. While, the **aminoglycoside**s were implicated in 13.71% to positive cases. The result also showed that, the usage

of chloramphenicol group was 8%, and this is lower than the percent mentioned by (Wageh,2013), In a survey of **chloramphenic**ol use in poultry farms in Kaduna State Nigeria, 21 farm authorities (20.0%) admitted the use of chloramphenicol as veterinary preparations **(Table, 5).**

About the **aminoglycosid**e uses in the daily veterinarian consumption is 4% ,but (Fathalrhman *et al*.,2016) reported that , the gentamicin residues were (25%) in raw milk samples and (Mohammed, 2015) in Gaza reported out of 95 positive results, aminoglycosides group was defined in 26 samples (27.36%), and Tsepo Ramatla *et al*.(2017) reported the streptomycin, 34%.On the other hand Sulphonamide group were 8% represent the regular consumption in the study but reported that the detection was 25.3%.

The value of chi – square calculated to signify the differences between all the mentioned phrase was (15.24), (15.20), (16.20), (19.82) with P-value (0.000) which is lower than the level of significant value (5%) These refer to the existence of differences statistically **table (6).**

Figure (7), the views of the distribution of the sample by the Yes I am (%8.0) and the Owners/Workers by (%92.0).

Figure (7), showed that 92% of antibiotics administration follow-up was done by the owners and workers. This may lead to misuses or extra-liable because only 20% of the owners adhere with the guidelines. Only 8% of the veterinarian continue the treatment by them self. This result agreement with (Sawant *et al*, 2005), who reported that in 93% of the farms, the owners administere antibiotics and untrained personnel. According to Katakweba *et al*. (2012), about 70% of dairy farm owners give the drugs to their animal. Komolafe (2003) and El Zuber *et al*. (2012) reported that the antibiotic abuse is one or perhaps the most important

cause of the high prevalence of drugs residues and resistance among bacteria that is mentioned by (Nisha, 2008). The presence of high levels of antibiotic residues in meat, may be the results of misuse and overuse of antibiotics which may cause microbial resistance.

The value of chi – square calculated to signify the differences between the do you treat the sick animals with your self or the owners / workers follow the antibiotics course was (17.64) with P-value (0.000) which is lower than the level of significant value (5%) These refer to the existence of differences statistically **table (7).**

There was a question (check the antibiotics residues after slaughtering) sample by the yes (%12.0) and no by (%88.0) and sometime by (%0.0) and I have no idea (%0.0) **figure (8).**

In Europe, the European Union currently uses a four-plate microbial inhibition test (4PT) to test for β-lactams, tetracyclines, chloramphenicol, macrolides, aminoglycosides, sulfonamides and quinolones.

A one-plate test (1PT) has been used in Belgium (it is simpler and less expensive than the 4PT, and provides extensive information), and sensitivity compared to the 4PT. Results were comparable for β-lactams but the 1PT was less sensitive to the other drug groups.

Kidney is the recommended tissue to test, since many drugs are excreted in urine, and will be found in the kidney. The test is less effective in meat, in which the possibility of detecting positive results is low. Despite the lack of sensitivity, the ease and cost of the 1PT makes this a useful tool, in conjunction with other screening methods, for testing kidneys for residues (Koenen-Dierick *et al.*, 1995)

Are there antibiotics that have been banned globally?

Figure (9) the views of the distribution of the age sample the yes is (%72.0) and no (%16.0) and **I have no idea** (%12.0). This result (72%) showed that there is awareness and only 12 % of veterinarians have no idea about drug restrictions in livestock.

The value of chi – square calculated to signify the differences between all the mentioned phrase was (41.25) with P-value (0.000) which is lower than the level of significant value (5%) These refer to the existence of differences statistically table (8).

In the **Diagram (10) there was a question** do you think there is a test to check antibiotic residues before slaughtering?

The result was, yes (%20.0) and no by (%36.0) and sometime by (%44.0) and the result for the second question Do you check the antibiotics residuce before slaughtering? Yes (0.0%), No was (96%) and I have no Idea was (4%) **Diagram (11),** it **was also labeled by this question** Do you check the antibiotics residues before slaughter.

This result evaluated the knowledge of the veterinarians about the presence of some test capable to detect the drug residuce for live animals and the result was only 20% of the veterinarian they answered by Yes.

The Live Animal Swab Test (LAST) was checked in calf urine from 30 calves dosed with twice the normal dose and confirmed by quantitative assays. LAST was 100% accurate in detecting Oxytetracycline when concentrations were above 4.3 μg/ml. When Oxytetracycline levels fell below 4.3 μg/ml, the drug was correctly detected in only 60% of samples; 20% gave false positive results, and 20% gave false negative results. While LAST was 100% accurate at detecting therapeutically effective levels of Oxytetracycline in calves, this method is not effective when

testing for lower levels of the drug, and should not be used for the purposes of residue avoidance testing (Triune and Upson ,1989).

On the other hand, there is no veterinarians who applied the drug residue test pre-slaughtering and the result was (96%) by No.

CONCLUSION AND RECOMMENDATIONS

Conclusion:

The result of screening test of meat showed detectable levels of antibiotic residues which may indicate the widespread of the antibiotic misuses in the farms and lack of the awareness of farmers regarding the recommended withdrawal periods of drugs and extra-label uses of antibiotics, the side effect should be avoided by treating the causes of this problem and to start from veterinarians and owner's awareness, to control the withdrawal period and misuse of antibiotics, and applying of the microbiological methods for screening the antibiotics because it's still useful and coast less for monitoring the animal's products especially for the large herds in developing countries to avoid the harmful of residues to human and animal's health and finally using the law and legalization to avoid the side effect on livestock and human.

Recommendations:

The research recommended that:

- Avoid the using of antimicrobials in the veterinary field without a veterinarian's prescription and the administration should be done exclusively under the supervision of veterinarians.
- Strict observation of antibiotic withdrawal periods.
- Reduce the unnecessary antibiotic use in livestock.
- Launching of awareness campaigns about human health hazards associated with antibiotic residues in food of animal origin by concerned authorities (related health departments, livestock authorities and health, educational organization).
- National monitoring of antimicrobial residues in foods and establishing of the maximum residue limits.

- Designing a quality system fit with our consuming culture, behavior and our economy status.

References

- **Ababio, P. F., and Adi, D. D. (2012).** Evaluating Food Hygiene Awareness and Practices of Food Handlers in the Kumasi Metropolis. *Internet Journal of Food Safety*, 14(2), 35-43.
- **Abbasi, M. M; Nemati, M; Babaei, H; Ansarin, M., and Nourdadgar, A. O. S. (2012**). Solid-phase Extraction and Simultaneous Determination of Tetracycline Residues in Edible Cattle Tissues Using an HPLC-FL method. *Iranian Journal of Pharmaceutical Research*: IJPR, 11(3), 781.
- **Abou-Arab, A. A. K. (2002).** Degradation of Organochlorine Pesticides by Meat Starter in Liquid Media and Fermented Sausage. *Food and Chemical Toxicology*, 40 (1), 33-41. Accessed August, 2010.
- **Abou-Raya, S. H; A. R. Shalaby, N. A. Salama; H. Emam and F. M. Mehaya. 2013.** Effect of ordinary cooking procedures on tetracycline residues in chicken meat. *J. Food Drug Anal*. 21:80–86).
- **Ackah, M; Agyemang, O; Anim, A. K; Osei, J; Bentil, N. O; Kpattah, L and Hanson, J. E. K. (2011).** Assessment of Groundwater Quality for Drinking and Irrigation: The Case Study of Teiman-Oyarifa Community, Ga East Municipality, Ghana. *Proceedings of the International Academy of Ecology and Environmental Sciences*, 1(3-4), 186.
- **Addisalem HB; Bayleyegn MZ; Bayleyegn MZ. (2012).** Tetracycline Residue Levels in Slaughtered Beef Cattle from Free Slaughterhouses in Central Ethiopia. *Global Veterinarian* 8: 546-554.
- **Addo, J; Smeeth, L., and Leon, D. A. (2007).** Hypertension in Sub-saharan Africa: *A Systematic Review.* Hypertension, 50 (6), 1012-1018.
- **Adil M. Salman, Hind A. El Nasri, and Intisar A.M. Osman, (2012).** Detection of Antibiotic Residues in Milk Using Delvo Test kit and Disc

Assay Methods in Khartoum State, Sudan.U of K. *J. Vet. Med. and Anim*. Prod.; Vol. 3: 3-15.

- **Aerts, M. M. L; Hogenboom, A. C. and Brinkman, U. A. Th. (1995).** Analytical Strategies for the Screening of Veterinary Drugs and Their Residues in Edible Products. *J. Chromatogr*. 667, 1-20.
- **Afoakwa, Emmanuel Ohene (2005).** "Enhancing the Quality of School Feeding Programs in Ghana." Unpublished Article. Legon: *Department of Nutrition and Food Science* (2005).
- **Aggelogiannopoulos, D. R. O. S. I. N. O. S; Drosinos, E. H., and Athanasopoulos, P. (2007).** Implementation of a Quality Management System (QMS) According to the ISO 9000 Family in a Greek Small-sized winery: *A Case Study. Food Control*, 18(9), 1077-1085.
- **Ågren, Olof. (1991).** Att hantera livsmedel – en orientering om livsmedelslagstiftningen. 8 ed. Stockholm: *Konsultförlaget. ISBN* 7005 024 4.
- **Agwuth, K.N. and A. MacGowan (2006).** Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J. Antimicrob*. Chemother. 58:256-65.
- **Aiello SE, Lines PR, Kehn CM. (2005).** Anthelmintics in: *the Merck Veterinary Manual. (9th End)* Co. Icon, USA, pp: 2111-2124.
- **Al-Aloul, M; Crawley, J; Winstanley, C; Hart, C. A; Ledson, M. J; and Walshaw, M. J. (2004).** Increased Morbidity Associated with Chronic Infection by an Epidemic *Pseudomonas Aeruginosa* Strain in CF Patients. *Thorax*, 59(4), 334-336.
- **Alder, K. (1998).** Making Things the Same: Representation, Tolerance and the End of the Ancien Régime in France. *Social Studies of Science*, 28(4), 499-545.

- **Aliu YO, (2004):** A paper presented on Veterinary Drug Residues in Nigeria‘s Food at National Awareness Training Programme on Food Contaminants and Residues. *Women Development Centre*, Kaduna, 6-7 May 2004 and NAFDAC Auditorium, Oshodi, Lagos, 20-21 May 2004. (s).
- **Alla, M. B. W; Mohamed, T.E and Abdelgadir, A.E.(2011)**. Detection of antibiotics residues in beef in Ghanawa Slaughterhouse, Khartoum State, Sudan. *African Journal of Food Science*. 5 (10), 574–580.
- **Alloway, B., and Ayres, D. C. (1997).** Chemical Principles of Environmental Pollution. CRC Press. Alternative to Enzyme Immunoassay Screening for Residues of two Sulfonamides in Pigs.
- **Ambrose, P. G; Bhavnani, S. M; Rubino, C. M; Louie, A; Gumbo, T; Forrest, A and Drusano, G. L. (2007).** Pharmacokinetics-pharmacodynamics of Antimicrobial Therapy: it's not Just for Mice Anymore. *Clinical Infectious Diseases*, 44(1), 79-86.
- **Ames, B. N. (1983).** Dietary Carcinogens and Anticarcinogens: Oxygen Radicals and Degenerative Diseases. *Science, 221(4617), 1256-1264. And Nutrition*, 37: 93-209.
- **Amsterdam, A. (1996).** Susceptibility Testing of Antibiotics in Liquid Media.In: Lorian, V. (ed.) Antibiotics in Laboratory Medicine. *Williams and Wilkins*, MA, USA, pp. 52-111.
- **Anadón, A; Martínez-LarraĖaga, M. R; Díaz, M. J; Fernández-Cruz, M.L; Martínez, M. A; Frejo, M. T; Martínez, M; Iturbe, J. and Tafur, M. (1999**). Pharamacokinetic Variables and Tissue Residues of Enrofloxacin and Ciprofloxacin in Healthy Pigs. *Am. J. Vet. Res.* 60, 1377-1382.
- **Angelillo-Scherrer, A; De Frutos, P. G; Aparicio, C; Melis, E; Savi, P; Lupu, F., and Collen, D. (2001).** Deficiency or Inhibition of Gas6 Causes

Platelet Dysfunction and Protects Mice Against Thrombosis. *Nature Medicine,* 7(2), 215.

- **Angelillo, I. F; Viggiani, N. M; Greco, R. M., and Rito, D. (2001a**). HACCP and Food Hygiene in Hospitals Knowledge, Attitudes, and Practices of Food-services Staff in Calabria, Italy. *Infection Control and Hospital Epidemiology,* 22(6), 363-369.
- **Angulo, F. J; Nargund, V. N., and Chiller, T. C. (2004).** Evidence of an Association Between Use of Anti-Microbial Agents in Food Animals and Anti-Microbial Resistance Among Bacteria Isolated From Humans and the Human Health Consequences of such Resistance. *Journal of Veterinary Medicine,* Series B, 51(8-9), 374-379.
- **Animals IV:** Pharmacokinetics of sulfamethazine in cattle following administration of an intravenous dose and three oral dosage forms. *J. Pharm*. Sci.66:619-623.
- **Antignac, J. P., *et al*. (2004):** Application of Hyphenated Mass Spectrometric Techniques to the Determination of Corticosteroid Residues in Biological Matrices.*Chromatographia,* 59, S13–S22.
- **Aranea. (2011).** BRC Globala standarden för livsmedelssäkerhet. [online]http ://www.kiwaaranea. se/ uploadedFiles/Aranea/Services/Certifiering/BRC%20info.pdf. [23April 2012].
- **Arias, T. M., and Lozano-Zambrano, F. H. (2008).** Sistemática, Biogeografíay Conservación de las Hormigas Cazadoras de Colombia. Instituto de Investigación de Recursos Biológicos Alexander von Humboldt. Bogotá, Colombia.
- **Arvanitoyannis, I. S., and Kassaveti, A. (2009).** HACCP and ISO 22000–A Comparison of the Two Systems. *HACCP and ISO* 22000, 1.

- **Ashworth, J., and Mackie, R. M. (1986).** A Quantitative Analysis of the Langerhans cell in Chronic Plaque Psoriasis. *Clinical and Experimental Dermatology*, 11(6), 594-599.
- **Ashworth, R. B; Epstein, R. L; Thomas, M. H., and Frobish, L. T. (1986).** Sulfamethazine blood/tissue correlation study in swine. *American journal of veterinary research*, 47(12), 2596-2603.- Authority, G. S. (2013). Personal Communication with Standard Documentation Department.
- **Authority, G. S. (2013).** Personal communication with standard documentation department.
- **Ayçiçek, H; Aydoğan, H; Küçükkaraaslan, A; Baysallar, M., and Başustaoğlu, A. C. (2004).** Assessment of the Bacterial Contamination on Hands of Hospital Food Handlers. *Food Control*, 15(4), 253-259.
- **Babapour, A; Azami, L., and Fartashmehr, J. (2012).** Overview of Antibiotic Residues in Beef and Mutton in Ardebil, North West of Iran. *World Applied Sciences Journal*, 19(10), 1417-1422.
- **Babington, R; Matas, S; Marco, M. P., and Galve, R. (2012).** Current Bioanalytical Methods for Detection of Penicillins. *Analytical and Bioanalytical Chemistry*, 403(6), 1549-1566.
- **Bacigalupo, A; Broccia, G; Corda, G; Arcese, W; Carotenuto, M; Gallamini, A., and Todeschini, G. (1995).** Antilymphocyte Globulin, Cyclosporin, and Granulocyte Colony-stimulating Factor in Patients with Acquired Severe Aplastic Anemia (SAA): *a Pilot Study of the EBMT SAA Working Party*. Blood, 85(5), 1348-1353.
- **Bánáti, D., and Lakner, Z. (2012).** Managerial Attitudes, Acceptance and Efficiency of HACCP Systems in Hungarian Catering. *Food control*, 25(2), 484-492.

- **Barbosa, J; Cruz, C; Martins, J; Manuel Silva, J; Neves, C; Alves, C., and Noronha Da Silveira, M. I. (2005).** Food poisoning by clenbuterol in Portugal. *Food additives and Contaminants*, 22(6), 563-566.
- **Bardic, A. (2001).** HACCP Ready. *Dairy Field*, 184(6).
- **Barrow, G.I. and Feltham, R.K.A. (1993).** Characters of Gram-positive bacteria. *In Cowan and Steel's Manual for the identification of Medical bacteria* (p. 52). Cambridge Univ. Press, New York, NY.
- **Bayarski, Y. (2006).** Antibiotics and Their Types, Uses and Side Effects. Retrievedfrom http://ezinearticles. com.
- **Baynes, R. E; Payne, M; Martin-Jimenez, T; Abdullah, A. R; Anderson, K. L; Webb, A. I., and Riviere, J. E. (2000).** Extralabel Use of Ivermectin and Moxidectin in Food Animals. *Journal of the American Veterinary Medical Association*, 217(5), 668-671.
- **Becker, H. J. (2000).** Findings from the Teaching, Learning, and Computing Survey. *Education Policy Analysis Archives*, 8, 51.
- **Bele C; C. T. Matea ; F. Dulf., and Mirela Miclean**. Determination of six sulfonamides in pork and beef meat by a new solid phase extraction and hplc - uv for detection. *Bulletin* USAMV-CN, 64/2007 (1-2).
- **Belloque, J; Garcia, M.C; Torre, M. and Marina, M.L., (2002)**. Analysis of soyabean proteins in meat products: a review. *Critical Reviews in Food Science and Nutrition*, 42(5), pp.507-532.
- **Berends, B. R; Van Den Bogaard, A. E. J. M., Van Knapen, F., and Snijders, J. M. A. (2001).** Veterinary Public Health: Human Health Hazards Associated with the Administration of Antimicrobials to Slaughter Animals: Part II. An Assessment of the Risks of Resistant Bacteria in Pigs and Pork. *Veterinary Quarterly*, 23(1), 10-21.

- **Berendsen, B; Stolker, L; de Jong, J; Nielen, M; Tserendorj, E; Sodnomdarjaa, R., and Elliott, C. (2010).** Evidence of Natural Occurrence of the Banned Antibiotic Chloramphenicol in Herbs and Grass. *Analytical and Bioanalytical Chemistry*, 397(5), 1955-1963.

- **Berendsen, A. M. (2013).** *Marine Painting Manual*. Springer Science and Business Media.
- **Berendsen, B; Pikkemaat, M; Römkens, P; Wegh, R; Van Sisseren, M., Stolker, L., and Nielen, M. (2013).** Occurrence of Chloramphenicol in Crops Through Natural Production by Bacteria in Soil. *Journal of Agricultural and Food Chemistry*, 61(17), 4004-4010.
- **Berendsen, B.J. and Nielen, M.W., 2013**. Selectivity in the sample preparation for the analysis of drug residues in products of animal origin using LC-MS. *TrAC Trends in Analytical Chemistry*, *43*, pp.229-239.
- **Bergström, M. and Hellqvist, R. (2004).** Kvalitets- och Miljöledning i livsmedelsbranschen. 2.ed. Uppsala: Bergström and Hellqvist AB.
- **Bernhardt, H. W., and Raschke, A. (1998).** Good Manfactuering Practice (GMP). IN Cane Sugar Factories. *In Proc S Afr Sug Technol Ass* (Vol. 1, No. 998, p. 72).
- **Bevill, R. F. (1984).** Factors Influencing the Occurrence of Drug Residues in Animal Tissues After the Use of Antimicrobial Agents in Animal Feeds. *J.Am. Vet. Med. Assoc*. 185, 1124-1126.
- **F. BEVILL, R., (1989).** Sulfonamide residues in domestic animals. *Journal of veterinary pharmacology and therapeutics*, 12(3), pp.241-252.
- **Bevill, R. F; G. D. Koritz, L. W. Dittert and D. W. Bourne (1977a).** Disposition of Sulfonamides in Food-Producing Animals V: Disposition of

Sulfathiazole in Tissue Urine, and Plasma of Sheep Following Intravenous Administration. *J. Pharm. Sci*.66:1297-1300.

- **Bevill, R. F; L. W. Dittert and D. W. Bourne. (1977b)**. Disposition of sulfonamides in foodproducing animals IV: Pharmacokinetics of sulfamethazine in cattle following administration of an intravenous dose and three oral dosage forms. *J. Pharm. Sci*. 66:619-623.
- **Beyene, T; and Tesega, B. (2014)**. Rational veterinary drug use: Its significance in public health. *Journal of Veterinary Medicine and Animal Health*, 6(12), 302-308.
- **Bjerklie, S. (1992).** HACCP in Your Plant: What HACCP is, what it isn't and how Your Operations Will be Affected. *Meat and Poultry*, 38(2), 14-22.
- **Black, W.D. (1984).** The use of antimicrobial drugs in agriculture. Can. J. Physiol. Pharmacol. 62(8): 1044-1048.
- **Block, E; Putman, D., and Zhao, S. H (1992).** Allium Chemistry: GC-MS Analysis of Thiosulfinates and Related Compounds from Onion, Leek, Scallion, Shallot, Chive, and Chinese Chive. *Journal of Agricultural and Food Chemistry*, 40(12), 2431-2438.
- **Bogaerts R., and Wolf F (1980).** A Standardized Method for the Detection of Residues of Anti-bacterial Substances in Fresh Meat.Fleischwirtschaft. 60: 672-674.
- **Boiral, O. (2012).** ISO 9000 and organizational effectiveness: A systematic review. *Quality Management Journal*, 19(3), pp.16-37.
- **Boison, J. O., and Keng, L. J. (1995).** Determination of Sulfadimethoxine and Sulfamethazine Residues in Animal Tissues by Liquid Chromatography and Thermospray Mass Spectrometry. *Journal of AOAC International*, 78(3), 651-658.

- **Boison, G; Schmitz, O; Mikheeva, L; Shestakov, S; Bothe, H (1996).** Cloning, Molecular Analysis and Insertional Mutagenesis of the Bidirectional Hydrogenase Genes from the Cyanobacterium Anacystis Nidulans. *FEBS letters*, 394(2), 153-158.
- **Boison, J. O; Nachilobe, P; Cassidy, R; Keng, L; Thacker, P. A; Peacock, A; Fesser, A. C; Lee, S; Korsrud, G. and Bulmer, W. S. (1996).** Determination of Trimethoprim and Sulphadoxine Residues in Porcinetissues and Plasma. *Can. J. Vet. Res.* 60, 281-287.
- **Booth, N. H; McDonald, L. E., and Jones, L. M. (1988).** Veterinary Pharmacology and Therapeutics (No. SF 915. J66 1988).
- **Boothe, N.H. and L. Donald. (1998).** Toxicology of Drug and Chemical Residues, In: Veterinary Pharmacology and Therapeutics, (6 Edn) *Iowa State University Press*, USA, pp: 1149-1195.
- **Boothe DM and Reevers PT. (2012.)** Pharmacology Introduction In: Aiello SE, Moses MA, Steigerwald MA (Eds) *The Merck Veterinary Manual*. Merck Publishing Group.
- **Botsoglou, N. A., and Fletouris, D. J. (2001).** Drug residues in foods: Pharmacology. *Food Safety and Analysis*, 23(1), 312-323.
- **Bovee, T. F. H., and Pikkemaat, M. G. (2009).** Bioactivity-based Screening of Antibiotics and Hormones. *Journal of Chromatography A*, 1216(46), 8035-8050.
- **Boxall, A. B; Blackwell, P; Cavallo, R; Kay, P., and Tolls, J. (2002).** The Sorption and Transport of a Sulphonamide Antibiotic in Soil Systems. *Toxicology letters*, 131(1-2), 19-28.
- **BRC Global Standards. (2011).** BRC Global Standard for Food Safety. 6. ed. London: TSO.ISBN 9780117069671.

- **Brown, TA. (2002).** Mutation, Repair and Recombination. In: Genomes. (2nd Edn) *Garland Science*, Manchester, UK
- **Bruhn, C. M. (1999).** Consumer Perceptions and Concerns About Food Contaminants. In Impact of Processing on Food Safety (pp. 1-7). *Springer*, Boston, MA.
- **Brynes, S. D; and Weber, N. E. (1996).** Residues of Veterinary Drugs and Mycotoxins in Animal Products.
- **Buncic, S. (2006).** Integrated Food Safety and Veterinary Public Health. *CABI International Publishing*, Wallingford, Oxfordshire, UK (ISBN 0-85199-908-5).
- **Bushra, R; Aslam, N., and Khan, A. Y. (2011).** Food-drug Interactions. *Oman Medical Journal*, 26(2), 77.
- **Butaye, P; Devriese, L. A., and Haesebrouck, F (2001).** Differences in Antibiotic Resistance Patterns of Enterococcus Faecalis and Enterococcus FaeciumStrains Isolated from Farm and Pet Animals. *Antimicrobial Agents and Chemotherapy*, 45(5), 1374-1378.
- **Buur, J; Baynes, R; Smith, G., and Riviere, J (2006).** Use of Probabilistic Modeling Wthin a Physio- logically Based Pharmacokinetic Model to Predict Sulfamethazine Residue Withdrawal Times in Edible Tissues in Swine. *Antimicrobial Agents and Chemotherapy*, 50(7), 2344-2351.
- **Cacciatore, G; Petz, M; Rachid, S; Hakenbeck, R., and Bergwerff, A. A. (2004).** Development of an Optical Biosensor Assay for Detection of β-lactam Antibiotics in Milk Using the Penicillin-binding Protein 2x. *Analytica Chimica Acta*, 520(1-2), 105-115.
- **Calderón, C. B., and Sabundayo, B. P. (2007).** Antimicrobial Classifications: Drugs for Bugs. *Antimicrobial Susceptibility Testing Protocols*, 7.

- **Granholm, C. (2017).** Social work in digital transfer: Blending services for the next generation. *Mathilda Wrede Institute Research Reports* 1/2016. Helsinki.
- **Canadian Food Inspection Agency (CFIA). (2014).** Chemical Residues. In: Meat Hygiene Manual of Procedures: Chapter 5-Sampling and Testing Procedures. Meat Hygiene Directives.
- **Cantoni, C., and Comi, G. (1997).** Changes in the Concentrations of Pesticide Residues in Foods and in Human Tissues Between 1960 and 1996. *Outlook on Agriculture*, 26(1), 47-52.
- **Capon, N; Farley, J. U., and Hoenig, S. (1990).** Determinants of Financial Performance: a Meta-Analysis. *Management Science*, 36(10), 1143-1159.
- **Cerniglia, C. E., and Kotarski, S. (1999).** Evaluation of Veterinary Drug Residues in Food for Their Potential to Affect Human Intestinal Microflora. *Regulatory Toxicology and Pharmacology*, 29(3), 238-261.
- **Chang Q; Wang W; Regev-Yochay G; Lipsitch M, and Hanage WP. (2014)** Antibiotics in agriculture and the risk to human health: how worried should we be? *Evolutionary Applications*, 8: 240-247.
- **Cháfer-Pericás, C; Maquieira, A., and Puchades, R. (2010).** Fast Screening Methods to Detect Antibiotic Residues in Food Samples. *TrAC Trends in Analytical Chemistry*, 29(9), 1038-1049.
- **Chen, V. B; Arendall, W. B; Headd, J. J; Keedy, D. A; Immormino, R. M; Kapral, G. J., and Richardson, D. C. (2010).** MolProbity: All-atom Structure Validation for Macromolecular Crystallography. Acta Crystallographica Section D: *Biological Crystallography*, 66(1), 12-21.
- **Chiesa, O. A; J. von Bredow; D. Heller; C. Nochetto; M. Smith; K. Moulton and M. Thomas. (2006a).** Use of Tissue-fluid Correlations to

Estimate Gentamicin Residues in Kidney Tissue of Holstein Steers. *J. Vet. Pharmacol*. Therap. 29:99-106.

- **Chiesa, O. A; J. von Bredow; M. Smith; D. Heller; R. Condon and M. H. Thomas. (2006b)**.Bovine Kidney Tissue/biological Fluid Correlation for Penicillin. *J. Vet. Pharmacol.*
- **Choma, I. M; Choma, A., and Staszczuk, K. (2002).** Determination of Flumequine in Milk by Thin-layer Chromatography-bioautography. *Journal of Liquid Chromatography and Related Technologies,* 25(10-11), 1579-1587.
- **Cinquina, A. L; Longo, F; Anastasi, G; Giannetti, L., and Cozzani, R. (2003).** Validation of a High-Performance Liquid Chromatography Method for the Determination of Oxytetracycline, Tetracycline, Chlortetracycline and Doxycycline in Bovine Milk and Muscle. *Journal of Chromatography A*, 987(1-2), 227-233.
- **Clement, R. P. 1995.** Preclinical Drug Metabolism Programs for Food-producing Animals. *Toxicol. Pathol*. 23(2): 209-216.
- **Code of Federal Regulations (CFR) (2006)** Food and Drug Administration.
- **Commission of the European Communities**. Directorate-General Employment, European **Commission. Directorate-General for Employment, and Social Affairs. Unit V/A. (1990).** Employment in Europe. Office for Official Publications of the European Communities. Compounds used in food-producing animals. http://www.fda.gov/downloads/
- **Concon, J. M. (1988).** Food Toxicology. Part A: Principles and Concepts; Part B: Contaminants and Additives. *Marcel Dekker Inc.Contaminants*, 23: 362-384.

- **Cooper, H; Lindsay, J. J; Nye, B., and Greathouse, S. (1998).** Relationships Among Attitudes about Homework, Amount of Homework Assigned and Completed, and Student Achievement. *Journal of Educational Psychology*, 90(1), 70.
- **Cooper, W. W; Seiford, L. M., and Zhu, J. (2004).** Data Envelopment Analysis. In Handbook on Data Envelopment Analysis (pp. 1-39). *Springer*, Boston, MA.
- **Corlett, R.T. (1998).** Frugivory and seed dispersal by vertebrates in the Oriental (Indomalayan) Region. *Biological reviews,* 73(4), pp.413-448.
- **Corlett, R. T. (2007).** The Impact of Hunting on the Mammalian Fauna of Tropical Asian Fforests. *Biotropica*, 39(3), 292-303.
- **Cotter, P. D; Stanton, C; Ross, R. P., and Hill, C. (2012).** The Impact of Antibiotics on the Gut Microbiota as Revealed by High Throughput DNA Sequencing. *Discovery Medicine*, 13(70), 193-199.
- **Craigmill, A. L., and Cortright, K. A. (2002).** Interspecies Considerations in the Evaluation of Human Food Safety for Veterinary Drugs. *AAPS PharmSci*, 4(4), 126-136.
- **Crawford, L.M. (1985).** The impact of residues on animal food products and human health. *Revue Scientifique et Technique de l'OIE (France).*
- **Crook, T. R; Ketchen Jr, D. J; Combs, J. G., and Todd, S. Y. (2008).** Strategic Resources and Performance: A meta-analysis. *Strategic Management Journal*, 29(11), 1141-1154.
- **Crooks, S.R.H; G.A. Baxter; M.C. O'Connor and C.T. Elliot. 1998a**. Immunobiosensor—an alternative to enzyme immunoassay screening for residues of two sulfonamides in pigs. *Analyst,* 123(12), 2755-2757.
- **Crooks, S. R; Fodey, T. L; Gilmore, G. R., and Elliott, C. T. (1998b).** Rapid screening for monensin residues in poultry plasma by a dry reagent

dissociation enhanced lanthanide fluoroimmunoassay. *Analyst*, 123(12), 2493-2496.

- **Crosby, J. (1991).** Synthesis of Optically Active Compounds: a Large Scale Perspective. *Tetrahedron*, 47(27), 4789-4846.
- **Cullor, J; Eenennaam, A; Gardner, I; Perani, L; Dellinger, J; Smith, W; Thompson, T; Payne, M; Jensen, L., and Guterbock, W., J.** Assoc. *Off Anal.Chem*. (1994) 77, 862-870.
- **CVM, (2006).** Guidance for industry 3. General principles for evaluating the safety of d 10 December 2007.
- **Dams, R; Huestis, M. A; Lambert, W. E., and Murphy, C. M. (2003):** Matrix Effects in Bio-analysis of Illicit Drugs with LC-MS/MS: Influence of Ionization Type, Sample Preparation and Biofluid. *Journal of the American Society of Mass Spectrometry*, 14, Case of Substances Having a MRL, the Sample is 1290–1294.
- **Darwish, W. S; Eldaly, E. A; El-Abbasy, M. T; Ikenaka, Y; Nakayama, S., and Ishizuka, M. (2013).** Antibiotic Residues in Food: the African Scenario. *Japanese Journal of Veterinary Research*, 61(Supplement), S13-S22.
- **Davis, J. L; Green, J. D., and Reed, A. (2009).** Interdependence with the environment: Commitment, interconnectedness, and environmental behavior. *Journal of environmental psychology*, 29(2), 173-180.
- **Dawit, D. (2010).** The Role of Regulatory Bodies in Ensuring Food Safety in Ethiopia-Status and Achievements of MoH.
- **Dayan, P. (1993).** Improving Generalization for Temporal Difference Learning: The Successor Representation. *Neural Computation*, 5(4), 613-624.DC, pp. 157.

- **De Brabander, H. F; Batjoens, P., and Van Hoof, J. (1992).** Determination of Thyreostatic Drugs by HPTLC with Confirmation by GC–MS. *Journal of Planar Chromatography*, 5, 124-130.
- **De Bukanski, B. W; Degroodt, J. M., and Beernaert, H. (1988).** A two-dimensional high-performance thin-layer chromatographic screening method for sulphonamides in animal tissues Identifizierung von sulfonamiden in geweben von schlachttieren mittels zweidimensionaler hochleistungsdünnschichtchromatographie. Zeitschrift für Lebensmittel-*Untersuchung und Forschung*, 187(3), 242-245.
- **De Ruig, W. G; Stephany, R. W., and Dijkstra, G. (1989).** Criteria for the Detection of Analytes in Test Samples. *Journal-Association of Official Analytical Chemists*, 72(3), 487-490.
- **De Wasch, K; Okerman, L; De Brabander, H; Van Hoof, J; Croubels, S., and De Backer, P. (1998).** Detection of Residues of Tetracycline Antibiotics in Pork and Chicken Meat: Correlation between results of screening and confirmatory tests. *Analyst*, 123(12), 2737-2741.
- **De Wasch, K; Brabander, H. B; Impens, S; Vandewiele, M., and Courtheyn, D. (2001).** Determination of Mercaptobenzimidazol and other Thyreostat Residues in Thyroid Tissue and Meat Using High-Performance Liquid Chromatography–mass Spectrometry. *Journal of Chromatography A*, 912(2), 311-317.
- **De Zutter, L; Koenen-Dierick, K. and van Hoof, J. (1985).** Detection of Antimicrobial Residues in Slaughtered Animals. II. Sensitivity of Some Detection Methods to Different Antibiotics. Vlaams Diergeneesk. Tijdschr. 54, 445-454.
- **Degroodt, J. M., de Bukanski, B. W., Beernaert, H., and Courtheyn, D. (1989).** Clenbuterol Residue Analysis by HPLC-HPTLC in Urine and

Animal Tissues Rückst and Sbestimmung Von Clenbuterol in Urin und Geweben Von Schlachttieren Mittels HPLC-HPTLC. *Zeitschrift für Lebensmittel-Untersuchung und Forschung*, 189(2), 128-131.

- **Degroodt, J. M., de Bukanski, B. W., De Groof, J., and Beernaert, H. (1991).** Cimaterol and clenbuterol residue analysis by HPLC-HPTLC in liver. *Zeitschrift für Lebensmittel-Untersuchung und Forschung*, 192(5), 430-432.
- **Desalegne A, Kelay B, Girma Z (2014)** Detection and Determination of Oxytetracycline and Penicillin G Antibiotic residue Levels in Bovine Bulk Milk from Nazareth Dairy Farms, Ethiopia. *Ethiop Vet J* 18: 1-15.
- **Dewdney, J. M; Maes, L; Raynaud, J. P; Blanc, F; Scheid, J. P; Jackson, T; Lens, S. and Verschueren, C. (1991)**. Risk Assessment of Antibiotic Residues of ù-lactams and Macrolides in Food Products with Regard to their Immuno-allergic Potential. *Food Chem. Toxic.* 29, 477-483.
- **Dey, B. P; Thaler, A. and Gwozdz, F. (2003).** Analysis of Microbiological Screen Data for Antimicrobial Residues in Food Animals. *J. Environm. Sci.Health* B38, 391-404.
- **Dickson, R. R., and Brown, J. (1994).** The Production of North Atlantic Deep Water: Sources, Rates, and Pathways. *Journal of Geophysical Research*: *Oceans*, 99(C6), 12319-12341.
- **Domènech, E; Vega, R; Ojanguren, I; Hernández, Á; Garcia-Planella, E; Bernal, I., and Gassull, M. A. (2008).** Cytomegalovirus Infection in Ulcerative Colitis: a Prospective, Comparative Study on Prevalence and Diagnostic Strategy. *Inflammatory Bowel Diseases*, 14(10), 1373-1379.
- **Donkor, J; Zhang, P; Wong, S; O'Loughlin, L; Dewald, J; Kok, B. P., and Reue, K. (2009).** A Conserved Serine Residue is Required for the Phosphatidate Phosphatase Aivity but not Transcriptional Coactivator

Functions of Lipin-1 and Lipin-2. *Journal of Biological Chemistry*, jbc-M109.

- **Doyle, M. E. (2006).** Veterinary drug residues in processed meats—potential health risk, FRI briefings. *Food Research Institute, University of Visconsin: Madison, WI, USA*, pp.148-196.
- **Drusano, G. L. (2007).** Pharmacokinetics and Pharmacodynamics of Antimicrobials. *Clinical Infectious Diseases*, 45(Supplement_1), S89-S95.
- **Dunn, O. J. (1964).** Multiple Comparisons Using Rank Sums. *Technometrics*, 6(3), 241-252.
- **Economy, E. C. (2010).** The River Runs Black: the Environmental Challenge to China's Future. *Cornell University Press*.
- **EFSA, P. (2007).** Scientific Opinion of the Panel on Plant Protection Products and their Residues on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil. *EFSA Journal* (2007), 622, 32.
- **EFSA, A. (2012).** Panel (EFSA Panel on Food Additives and Nutrient Sources Added to Food), 2012. Guidance for Submission for Food Additive Evaluations. *EFSA Journal* 2012; 10 (7): 2760, 60 pp.
- **Eisele, C; Nevsky, A. Y., and Schiller, S. (2009).** Laboratory Test of the Isotropy of Light Propagation at the 10− 17 Level. *Physical Review Letters*, 103(9), 090401.
- **Ekene V. Ezenduka and Chinyere Ugwumba. (2012)**. Antimicrobial residues screening in pigs and goats slaughtered in Nsukka Municipal abattoir, Southeast Nigeria. *African Journal of Biotechnology* Vol. 11(57), pp. 12138-12140, 17 July, 2012.
- **El Zubeir, I.E.M; Kiessling, S ; Kutzer, P; Wieler, L.H. and ElOwni, O.A.O. (2012).** Characterization of tetracycline resistant Staphylococcus

aureus isolated from bovine mastitis in Khartoum State, Sudan. University of Khart. *J. Vet. Med. and Anim. Prod.*, 3 (2): 53-64.

- **Elliot, A. J., and Harackiewicz, J. M. (1996).** Approach and Avoidance Achievement Goals and Intrinsic Motivation: A mediational analysis. *Journal of Personality and Social Psychology*, 70(3), 461.
- **Elliott, C. T; Baxter, G. A; Hewitt, S. A; Arts, C. J; van Baak, M; Hellenäs, K. E., and Johannson, A. (1998).** Use of Biosensors for Rapid Drug Residue Analysis without Sample Deconjugation or Clean-up: a possible way forward. *Analyst*, 123(12), 2469-2473.
- **El-Makawy, A; Radwan, H. A; Ghaly, I. S., and El-Raouf, A. A. (2006).** Genotoxical, Teratological and Biochemical Effects of Anthelmintic Drug Oxfendazole Maximum Residue Limit (MRL) in Male and female mice. *Reproduction Nutrition Development*, 46(2), 139-156.
- **EPA, U. (2007).** Guidance on the Use of Models and other Analyses for Demonstrating Attainment of Air Quality Goals for Ozone, PM2. 5, and Regional haze. US Environmental Protection Agency, Office of Air Quality Planning and Standards.
- **Er. B; Onurdag, F. K; Demirhan, B; Ozgacar, S. O; Oktem, A. B; Abbasoglu, U. (2013).** Screening of quinolone antibiotic residues in chicken meat and beef sold in the markets of Ankara, Turkey. *Poultry Science*. 92, 2212–2215.
- **Eriksson, L. I. (2009).** *Miller's Anesthesia*: Elsevier Health Sciences. 1 (Vol. 1).
- **Erkyihun, T. (2010).** The role of Quality and Standards Authority of Ethiopia (QSAE) in ensuring food safety.
- **European Commission. Directorate-General for Economic, and Economic Policy Committee of the European Communities. (2006).** The

impact of ageing on public expenditure: projections for the EU-25 Member States on pensions, healthcare, long-term care, education and unemployment transfers (2004-50). *Office for Official Publications of the European Communities*.

- **European Community (EC) (2001)** Notice to applicant and note for guidance. Establishment of maximum residue limits for residue of veterinary medicinal products in food stus of animal origin pp. 4-10.
- **Eyssen, H; Vanderhaeghe, H., and De, P. S. (1971).** Effect of polybasic antibiotics and sulfaguanidine on absorption and excretion of cholesterol and bile salts. *In Federation proceedings* (Vol. 30, No. 6, pp. 1803-1807).
- **Ezenduka, E. V., and Ugwumba, C. (2012).** Antimicrobial residues screening in pigs and goats slaughtered in Nsukka Municipal abattoir, Southeast Nigeria. *African Journal of Biotechnology*, 11(57), 12138-12140.
- **Faergemand, J., and Jespersen, D. (2004).** ISO 22000 to ensure integrity of food supply chain. *ISO Management Systems*, 5, 1-24.
- **Færgemand , J. (2008).** The ISO 22 000 series: global standards for safe food supply chains.*ISO Management Systems*,8(3), 4-7.
- **Fajt, V. R. (2003).** Regulatory considerations in the United States. The Veterinary clinics of North America. *Food animal practice*, 19(3), 695-705.
- **FAO (2005).** Food Safety Risk Analysis. Part I - An Overview and Framework Manual. *Provisional Edition FAO Rome*, June 2005.
- **FAO/WHO (1995).** Expert Consultation. Geneva, March 1995 (available at ftp://ftp.fao.org/es/esn /food/Risk_Analysis.pdf).
- **FAO/WHO (2005).** Practical actions to promote food safety. Regional Conference on food safety for Africa. Harare, Zimbabwe, 3-6 October 2005.
- **Faridah, S; I. Zamri, C.S; Tan, H.K ;Wong, E.A;Engku Azahan, A.R. Gayah and S. Ahmad Tarmizi (2004).** Development of direct competitive

enzyme immunoassay kit for the detection of streptomycin residues in chicken meat and feed. *J. Trop. Agric. Fd. Sci*.32:179-186.

- **Farzianpour, F; Namati, A; Raeisi, A. R; Torabi, M; Rahmani, K; Manafi, F., and Mehrabany, K. B. (2014).** implementation of hazard analysis and critical control points requirements in nutrition departments of selected hospitals in iran. *American Journal of Agricultural and Biological Sciences*, 9(2), 218.
- **Fathalrhman, A. N; Osman, A. A. A; Idres, M. A., and Sid-Ahmed, M. A. (2016**). *Autonomous Navigation in Dynamic Environments* (Doctoral dissertation, Sudan University of Science and Technology).
- **FDA, U. (1999).** Guidance for industry: population pharmacokinetics. *Rockville (MD)*: FDA.
- **FDA, (2005a).** Withdrawal of approval of Bayer Corporation's new animal drug Application (NADA) 140-828 (Baytril) Docket No. 2000N-1571 www.fda.gov/AnimalVeterinary/ SafetyHealth/RecallsWithdrawals/ucm042004.htm Accessed August, 2010.
- **FDA, (2005b).** Chapter: Post-approval monitoring of animal drugs, feeds and devices. Subject. Illegal residues in meat, poultry, seafood and other animal derived foods.Implementation date 08/01/2005. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/Compliance.
- **FDA, (2010)**. The judicious use of medically important antimicrobial drugs in food-producinganimals.http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/ *Guidance forIndustry*/UCM216936.pdf. Accessed August, 2010.

- **FDA-TDS, (2008).** Total diet study http://www.fda.gov/Food/FoodSafety/ Food Contaminants Adulteration/TotalDietStudy/default.htm Accessed August, 2010.
- **FDA-TDS, (2009)**. Total Diet Study- TDS food/analyte matrix. http://www.fda.gov/Food /FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/ucm184970.htm. Accessed August, 2010.
- **Fedeniuk, R.W. (1988).** Oxytetracycline degradation in model meat processing systems. Ph.D.
- **Federal Environmental Protection Authority (FEPA) (2004).** Environmental Impact Assessment Guideline on Pesticides. Addis Ababa, Ethiopia.
- **Feglo, P., and Sakyi, K. (2012).** Bacterial contamination of street vending food in Kumasi, Ghana. *Journal of Medical and Biomedical Sciences*, 1(1), 1-8.
- **Fernández, D. G., Mancipe, L. C., and Fernández, D. C. (2010).** Intoxicación por organofosforados. *Revista Med*, 18(1), 84-92.
- **Fidel, T., and Milagro, R. (2006).** Methods for rapid detection of chemical and veterinary drug residues in animal food. *Trends in Food ScienceandTechnology*, 17(9), 482-489.
- **FL (Ed) CRC press**, Inc, Florida, USA.flumequine in broiler serum and muscle. Anal. Chim. Acta. 586:312-318.fluoroimmunoassay. *The Analyist* 123:2493-2496.
- **Fodey, T. L; Crooks, S. R; Elliott, C. T., and McCaughey, W. J. (1997).** Comparison of porcine urine and bile as matrices to screen for the residues of two sulfonamides using a semi-automated enzyme immunoassay. *Analyst*, 122(2), 165-168.

- **Fodey, T. L; Crooks, S; Elliott, C. T. and McCaughey, W. (1997).** Comparison of Porcine Urine and Bile as Matrices to Screen for the Residues of two Sulfonamides Using a Semi-automated Enzyme Immunoassay. *Analyst* 122, 165-168.
- **Food Additives and Contaminants (FAC, 2010)** screening methods for detection of antibiotic residues in slaughter animals: comparison of the EU-four plate method, the Nouws Antibiotic Test and the Premi Test (applied to muscle and kidney). *Food Additives and Contaminants,* 2010, 28 (1), pp.26.
- **Food Safety Authority of Ireland (FSAI) (2007)** Prudent use of medicines, pesticides and chemicals on farms.
- **Tam CC; Rodrigues LC; Viviani L., *et al*., (2012)** longitudinal study of infectious intestinal disease in the UK (IID2 study)**:** incidence in the community and presenting to general practice Gut (2012); 61:69-77 *FoodContaminantsAdulteration*/TotalDietStudy/default.htm Accessed August, 2010.
- **Foster W, Beecroi ML (2014)** Chemical Exposures and Human Fertility. Infertility Awarness Association of Canada.
- **Psomas, E. L., and Fotopoulos, C. B. (2009).** The impact of "soft" and "hard" TQM elements on quality management results. *International Journal of Quality and Reliability Management*, 26(2), 150-163.
- **Franek, M., and Hruska, K. (2005).** Antibody based methods for environmental and food analysis: a review. *Veterinarni Medicina*, 50(1), 1-10.
- **FSIS,** the nationwide microbiological baseline data collection program: young chicken survey, (2007), full report available online at http. www. fsis. usda. gov/ PDF/ Baseline _ Data _ Young _ Chicken .

- **FSIS-NRP, (2008).** Food Safety and Inspection Program. 2008 National Residue Program Sampling Plans http://www.fsis.usda.gov/PDF/ 2008_Blue_Book_Part1.pdf. Accessed August, 2010.
- **FSIS-NRP,(2009).** Food Safety and Inspection Service. 2009 FSIS National Residue Program Scheduled Sampling Plans. http://www.fsis.usda.gov/PDF/ 2009_Blue_Book.pdf. Accessed July 2010
- **Furusawa, K. (2000).** U.S. Patent No. 6,161,035. Washington, DC: U.S. Patent and Trademark Office.
- **Garber, E. A. (2008).** Detection of melamine using commercial enzyme-linked immunosorbent assay technology. *Journal of food protection*, 71(3), 590-594.
- **Galer, D. M., and Monro, A. M. (1996).** The safety assessment of drug residues at injection sites. *Journal of veterinary pharmacology and therapeutics*, 19(4), 312-312.
- **Gamhewage, B; Jayasinghe-Mudalige, U.K; Edirisinghe, J.C; Mendis, M.S.S; Perera, D.A.M; Udugama, J.M.M. and Herath, H.M.L.K. (2013).** Production and marketing policies in paddy sector in Sri Lanka: the farmer perceptions. In ISAE 2013. Proceedings of the International Symposium on Agriculture and Environment 2013, 28 November 2013, *University of Ruhuna, Sri Lanka* (pp. 572-576). Faculty of Agriculture, University of Ruhuna.
- **Garayoa, R., Vitas, A. I., Díez-Leturia, M., and García-Jalón, I. (2011).** Food safety and the contract catering companies: Food handlers, facilities and HACCP evaluation. *Food Control*, 22(12), 2006-2012.
- **Garber, E. A. E. (2008).** Detection of melamine using comercial enzyme-Linked immunosorbent assay technology. *Journal of food protection*, 71(3), 590-594.

- **Gaudin, V; Cadieu, N., and Maris, P. (2003).** Inter-laboratory studies for the evaluation of ELISA kits for the detection of chloramphenicol residues in milk and muscle. *Food and agricultural immunology*, 15(3-4), 143-157.
- **Gaudin, E; Tencé, S; Weill, F; Rodriguez Fernandez, J., and Chevalier, B. (2008).** Structural and magnetocaloric properties of the new ternary silicides Gd6M5/3Si3 with M= Co and Ni. *Chemistry of Materials*, 20(9), 2972-2979.
- **Gaudin, V; Juhel-Gaugain, M; Mortain, J. P., and Sanders, P. (2008).** AFNOR validation of Premi Test, a microbiological-based screening tube-test for the detection of antimicrobial residues in animal muscle tissue.*Food Additives and Contaminants*, 25(12), 1451-1464.
- **Gaudin, C; Simkin, M; White, D. J., and O'Loughlin, C. D. (2010)**. Experimental investigation into the influence of a keying flap on the keying behaviour of plate anchors. In The Twentieth International Offshore and Polar Engineering Conference. *International Society of Offshore and Polar Engineers*.
- **Gaugain, M., and Abjean, J. P. (1996).** High-performance thin-layer chromatographic method for the fluorescence detection of three nitroimidazole residues in pork and poultry tissue. *Journal of Chromatography* A, 737(2), 343-346.
- **Gehring, N. H; Kunz, J. B; Neu-Yilik, G; Breit, S; Viegas, M. H; Hentze, M. W., and Kulozik, A. E. (2005).** Exon-junction complex components specify distinct routes of nonsense-mediated mRNA decay with differential cofactor requirements. *Molecular cell*, 20(1), 65-75.
- **Gerald, B. L., and Perkin, J. E. (2003).** Position of the American Dietetic Association: Food and water safety. *Journal of the Academy of Nutrition and Dietetics*, 103(9), 1203.

- **Giguere, M. (2006).** Thinking as they create: Do children have similar experiences in dance and in language arts. *Journal of Dance Education*, 6(2), 41-47.
- **Gikas, A; Kritsotakis, E. I; Maraki, S; Roumbelaki, M; Babalis, D; Scoulica, E., and Tselentis, Y. (2007).** A nosocomial, foodborne outbreak of Salmonella Enterica serovar Enteritidis in a university hospital in Greece: the importance of establishing HACCP systems in hospital catering. *Journal of Hospital Infection*, 66(2), 194-195.
- **Gikas, P., and Mokbel, K. (2007).** Management of gynaecomastia: an update. *International journal of clinical practice*, 61(7), 1209-1215.
- **Gillian C (2003)** Avoiding drug carry over during feed processing and delivery. *FDA Veterinarian Newsletter* 6: 30-45.
- **Gildow, E.M., Fourt, D.L. and Shaw, A.O., (1938).** Sulfanilamide in the treatment of streptococcic mastitis. *Journal of Dairy Science*, 21(12), pp.759-766.
- **Gips, M., and Soback, S. (1996).** Norfloxacin nicotinate pharmacokinetics in unwearied and weaned calves. *Journal of veterinary pharmacology and therapeutics*, 19(2), 130-134.
- **Global and Local (2005).** Food Safety around the World Center for Science in the Public Interest June 2005 Washington, D.C. 20009- 5728. p. 5.
- **Gooden, W. E; Du, Y; Ahluwalia, R., and Day, R. A. (1994).** The Separation of Biologically Active Diastereomers of Zwitterionic β-Lactams by Anion Exchange Chromatography. *Analytical letters*, 27(11), 2153-2169.
- **Gooding, R.Z. and Wagner III, J.A. (1985).** A meta-analytic review of the relationship between size and performance: The productivity and efficiency of organizations and their subunits. *Administrative science quarterly*, pp.462-481.

- **Gormley, Andrew M; David M. Forsyth;Peter Griffioen; Michael Lindeman, David SL Ramsey; Michael P. Scroggie, and Luke Woodford**. "Using presence-only and presence–absence data to estimate the current and potential distributions of established invasive species." *Journal of Applied Ecology* 48, no. 1 (2011): 25-34.
- **Greig, J. D., and Lee, M. B. (2012).** A review of nosocomial norovirus outbreaks: infection control interventions found effective. *Epidemiology and Infection*, 140(7), 1151-1160.
- **Griffith, C. (2006).** HACCP and the management of healthcare associated infections: are there lessons to be learnt from other industries? *International Journal of Health Care Quality Assurance*, 19(4), pp.351-367.
- **Grugel, C., and Wallmann, J. (2004).** Antimicrobial Resistance in Bacteria from Food-producing Animals. Risk Management Tools and Strategies. *Journal of Veterinary Medicine*, Series B, 51(8-9), 419-421.
- **Guardabassi, L. and Dalsgaard, A., (2004).** Occurrence, structure, and mobility of Tn1546-like elements in environmental isolates of vancomycin-resistant enterococci. *Appl. Environ. Microbiol*., 70(2), pp.984-990.
- **Guest, G. B., and Paige, J. C. (1991).** The magnitude of the tissue residue problem with regard to consumer needs. *Journal of the American Veterinary Medical Association (USA)*.
- **Gulf Research Center, (2006).** Green Gulf Report. Gulf Research Center, Dubai.
- **Gustafson, G. M. (1993).** Effects of daily exercise on the health of tied dairy cows. *Preventive veterinary medicine*, 17(3-4), 209-223.
- **H. Malisch *et al*., (1988**). "Determination of residues of chemotherapeutic and antiparasitic drugs in food stuffs of anomaly origin with HPLC and UV-Vis diodearray detection*" J. Liq. Chromatogr*., 11 (13), 2801–2827.14.

- **Haagsma, N. (1985).** Rapid thin-layer chromatographic screening method for the detection of five sulfonamides in swine tissues: Collaborative study. *Zeitschrift für Lebensmittel-Untersuchung und Forschung*, 181(1), 45-46.
- **Haagsma, N. and Mengelers, M. J. (1989)**. A Rapid fluorimetric Screening Method for Chlortetracycline, Oxytetracycline and Tetracycline in Pig Meat and Kidney Tissues. Z. Lebensm. Unters. *Forsch*. 188, 227-231.
- **Haasnoot, W; Gerçek, H; Cazemier, G., and Nielen, M. W. (2007)**. Biosensor immunoassay for flumequine in broiler serum and muscle. *Analytica chimica acta*, 586(1-2), 312-318.
- **Hagren, V; Connolly, L; Elliott, C. T; Lövgren, T., and Tuomola, M. (2005**). Rapid screening method for halofuginone residues in poultry eggs and liver using time-resolved fluorometry combined with the all-in-one dry chemistry assay concept. *Analytica chimica acta*, 529(1-2), 21-25.
- Screening of Antibiotics Residues in Poultry Meat by Microbiological Methods. Bull. University of Agricultural Sciences and Veterinary Medicine, *Veterinary Medicine* (2013), 70(1), 77–82.
- **Hala, I., M., S. (2006).** *Residues of Antibiotic in Poultry Meat*. Thesis of master's degree (M. V. Sc.) in Preventive Medicine, Faculty of Veterinary Medicine, University of Khartoum.
- **Hammett-Stabler, C. A; Pesce, A. J., and Cannon, D. J. (2002**). Urine drug screening in the medical setting. *Clinica Chimica Acta*, 315(1-2), 125-135.
- **Hanekom, M; Mata, D; van Pittius, N. G; van Helden, P. D; Warren, R. M., and Hernandez-Pando, R. (2010).** Mycobacterium tuberculosis strains with the Beijing genotype demonstrate variability in virulence associated with transmission. Tuberculosis, 90(5), 319-325**.**

- **Heller, D. A; Jeng, E. S; Yeung, T. K; Martinez, B. M; Moll, A. E; Gastala, J. B., and Strano, M. S. (2006).** Optical detection of DNA conformational polymorphism on single-walled carbon nanotubes. *Science*, 311(5760), 508-511.
- **Heritage, J, Ransome, N., Chambers, P.A. and Wilcox, M.H. (2001)**. A comparison of culture and PCR to determine the prevalence of ampicillin-resistant bacteria in the faecal flora of general practice patients. *Journal of Antimicrobial Chemotherapy*, 48: 287-289.
- **Hewitt, W. (2012).** Theory and application of microbiological assay. Elsevier.
- **Hill, T; Marquez, L; O'Connor, M., and Remus, W. (1994**) Artificial neural network models for forecasting and decision making. *International journal of forecasting*, 10(1), 5-15.
- **Hoff, W.S; Bonadies, J.A; Cachecho, R. and Dorlac, W.C. (2011).** East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures. *Journal of Trauma and Acute Care Surgery*, 70(3), pp.751-754.
- **Huet, B; L'Hostis, V; Miserque, F., and Idrissi, H. (2005).** Electrochemical behavior of mild steel in concrete: Influence of pH and carbonate content of concrete pore solution. *Electrochimica Acta*, 51(1), 172-180.
- **Human Health, Department of Animal and Veterinary Sciences, College of Agricultural and Marine Sciences, Sultan Qaboos University, PO Box 34** Al-Khoud, Muscat, Sultanate of Oman.
- **Hunter, J. E., and Schmidt, F. L. (2004).** Methods of meta-analysis: Correcting error and bias in research findings. Sage.

- **Hussein, M. A., and S. Khalil. 2013.** Screening of some antibiotics and anabolic steroids residues in broiler fillet marketed in El-Sharkia Governorate. *Life Sci. J*. 10:2111–2118.
- **IARC** Working Group on the Evaluation of Carcinogenic Risks to Humans, and World Health Organization. (1987). Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42 (Vol. 7).
- **Ibrahim A, Junaidu A, Garba M (2009)** Multiple antibiotic residues in meat from slaughtered cattle in Nigeria. *He Internet Journal of Veterinary Medicine* 8: 1.
- **IDF,(1995).** Milk and Milk Products: Guidance on Sampling. Interna-tional Dairy Federation, Standard 50C, Brussels, Belgium.
- **Inge, H. and George, P. (2006)**. Antibiotics in Milk. Wageningen University Thesis Project
- **T Kadim, I. (2014).** Determination of Chemical Contaminates of Meat and Meat Products Which Threaten Human Health.
- **Isik, A; Alimoglu, O; Okan, I; Bas, G; Turgut, H., and Sahin, M. (2008).** Dieulafoy lesion in the stomach. Case reports in gastroenterology, 2(3), 469-473.
- **Isik, M; Sardon, H., and Mecerreyes, D. (2014).** Ionic liquids and cellulose: dissolution, chemical modification and preparation of new cellulosic materials. *International journal of molecular sciences*, 15(7), 11922-11940.
- **ISO, (2011).** Conformity Assessment: Requirements for bodies providing audit and certification of management systems. Isodelen,Alla certifierade företag. http://isodelen.se/index.aspx. [online]
- **Isoherranen, N. and Soback, S. (1999)**. Chromatographic methods for analysis of aminoglycoside antibiotics. *J. AOAC. Int*. 82, 1017-1045.

- **J. Pharm. Sci. (2005).** Administration of an Intravenous Dose and Three Oral Dosage Forms. Safety for Africa. Harare, Zimbabwe, 66:619-623. 3-6 October 2005.
- **Jabbar, A., (2004)**. Microbiological evaluation of antibiotic residues in meat, milk and eggs. M.Sc. Thesis. University of Agriculture Faisalabad, Pakistan.
- **Jabbar, M. A., and Grace, D. (2012).** Regulations for safety of animal source foods in selected Sub-Saharan African countries: Current status and their implications. *The Safe Food,* Fair Food Project International Livestock Research Institute: Nairobi, Kenya.
- **Jacela, J. Y; DeRouchey, J. M; Tokach, M. D; Goodland, R. D; Nelssen, J. L; Renter, D. G., and Dritz, S. S. (2009).** Feed additives for swine: Fact sheets–carcass modifiers, carbohydrate-degrading enzymes and proteases, and anthelmintics. *Journal of Swine Health and Production*, 17(6), 325-332.
- **Jafari, M; T. Khayamian, V. Shaer and N. Zarei(2000)**. Determination of veterinary drug residues in chicken meat using corona discharge ion mobility, Spectro. *Anal. Chim. Acta*., 581: 147-153.
- **Javadi, A; H. Mirzaie, and S. Khatibi. (2011)**. Effect of roasting, boiling and microwaving cooking methods on Enrofloxacin residues in edible tissues of broiler. *Afr. J. Pharm. Pharmacol*. 5:214–218).
- **Jensen, H.H; Unnevehr, L.J. and Gomez, M.I., (1998).** Costs of improving food safety in the meat sector. *Journal of agricultural and applied economics*, 30(1), pp.83-94.
- **Jiang, H; Ding, S; Li, J; An, D; Li, C. and Shen, J., (2006).** Residue depletion of tilmicosin in cattle after subcutaneous administration. *Journal of agricultural and food chemistry*, *54*(14), pp.5208-5213.

- **Joint FAO/WHO Expert Committee on Food Additives (JECFA) (2013)** Residue evaluation of certain veterinary drugs. 8th Meeting, FAO/ JECFA Monographs, pp. 15.
- **Johnston, D.S; Wright, W.W; Shaper, J.H; Hokke, C.H; Van den Eijnden, D.H. and Joziasse, D.H., (1998).** Murine sperm-zona binding, a fucosyl residue is required for a high affinity sperm-binding ligand a second site on sperm binds a nonfucosylated, β-galactosyl-capped oligosaccharide. *Journal of Biological Chemistry*, 273(4), pp.1888-1895.
- **Jones, F. T., and Ricke, S. C. (2003**). Observations on the history of the development of antimicrobials and their use in poultry feeds. *Poultry science*, 82(4), 613-617.
- **Jones, S. A. (2014).** Evaluation of Pre-harvest Screening for Antibiotics and Flunixin Meglumine in Cattle.
- **Jordbruksverket, S.J.V., (2011).** Hästar och anläggningar med häst 2010. Resultat från en intermittent undersökning. Rapport JO, 24.
- **Jukes, D. (2000).** The role of science in international food standards. *Food Control*, 11(3), 181-194.
- **Kaartinen, L; Pyörälä, S; Moilanen, M. and Räisänen, S. (1997).** Pharmacokinetics of enrofloxacin in newborn and one-week-old calves.*J. Vet. Pharmacol. Therap*. 20, 479-482.
- **Kaartinen, L; Salonen, M; Älli, L. and Pyörälä, S. (1995):** Pharmacokinetics of enrofloxacin after single intravenous, intramuscular and subcutaneous injections in lactating cows. *J. Vet. Pharmacol. Therap*. 18, 357-362.
- **Kaartinen, V; Voncken, J. W; Shuler, C; Warburton, D; Bu, D; Heisterkamp, N., and Groffen, J. (1995).** Abnormal lung development and

cleft palate in mice lacking TGF–β3 indicates defects of epithelial–mesenchymal interaction. *Nature genetics*, 11(4), 415.

- **Kaartinen, V; Cui, X. M; Heisterkamp, N; Groffen, J., and Shuler, C. F. (1997**). Transforming growth factor-β3 regulates transdifferentiation of medial edge epithelium during palatal fusion and associated degradation of the basement membrane. *Developmental dynamics*: an official publication of the American Association of Anatomists, 209(3), 255-260.
- **Kadim, I. T; Mahgoub, O; Al-Marzooqi, W; Khalaf, S. K; Mansour, M. H; Al-Sinani, S. S. H., and Al-Amri, I. S. (2009).** Effects of electrical stimulation on histochemical muscle fiber staining, quality, and composition of camel and cattle Longissimus thoracis muscles. *Journal of food science*, 74(1), S44-S52.
- **Kaneene, J. B. and Miller, R. (1997).** Problems associated with drug residues in beef from feeds and therapy. *Rev. Sci. Tech. Off. Int. Epiz*.16, 694-708.
- **Kaneene, J. B; Ross, W. A., and Miller, R. (1997).** The Michigan equine monitoring system. II. Frequencies and impact of selected health problems. *Preventive veterinary medicine*, 29(4), 277-292.
- **Kang'ethe, E K; Arimi, S M; Kioko, P M. (2011**) Safety of animal source foods in Kenya – A situational analysis. *Draft report submitted to ILRI*, Nairobi, Kenya.
- **Karr, K. J; Maretzki, A. N., and Knabel, S. J. (1994**). Meat and Poultry Companies Assess USDA's Hazard Analysis and Critical Control Point System. *Food Technology* (USA).
- **Katz, S. K., and Ward, P. M. L. (2004).** Antibiotic and Hormone Residues in Foods and their Significance. In Toxins in Food (pp. 283-298). *CRC Press*.

- **Keener, C. S. (1999).** *A Commentary on the Gospel of Matthew*. Wm. B. Eerdmans Publishing.
- **Kehinde, O. G; Junaidu, K; Mohammed, M., and AbdulRahman, A. M. (2012).** Detection of antimicrobial drug residues in commercial eggs using Premi Test.*Int J Poult Sci*,11(1), 50-4.
- **Kennedy, D. G; Cannavan, A., and McCracken, R. J. (2000**). Regulatory problems caused by contamination, a frequently overlooked cause of veterinary drug residues. *Journal of Chromatography A*, 882(1-2), 37-52.
- **Kennedy, J. A; Troup, G. J; Pilbrow, J. R ; Hutton, D. R; Hewitt, D; Hunter, C. R., and Jones, G. P. (2000).** Development of seed polyphenols in berries from Vitis vinifera L. cv. Shiraz. *Australian Journal of Grape and Wine Research*, 6(3), 244-254.
- **Khandke, S. S., and Mayes, T. (1998).** HACCP implementation: a practical guide to the implementation of the HACCP plan. *Food control*, 9(2-3), 103-109.
- **Kiangkitiwan, B; Doppalapudi, A; Fonder, M; Solberg, K., and Bohner, B. (2008**). Levofloxacin-induced delirium with psychotic features. *General hospital psychiatry*, 30(4), 381-383.
- **Kilinc, B., and Cakli, S. (2008).** Screening for antibiotic residues in the trout by the Four Plate test, Premi test and ELISA test. *European Food Research and Technology*, 226(4), 795-799.
- **Kim, D. O; Jeong, S. W., and Lee, C. Y. (2003).** Antioxidant capacity of phenolic phytochemicals from various cultivars of plums. *Food chemistry*, 81(3), 321-326.
- **Kirbiš, A; Marinšek, J. and Flajs, V.C.** (2005): Introduction of the HPLC method for the determination of quinolone residues in various muscle tissues. Biomedical Chromatography, 19,259–265.

- **Kirk - Othmer.,** "*Encyclopedia of chemical Technology* Vol.2, (Alkoxides, Metal to Antibiotics) A Wiley – *Inter science publication*, third edition. (1978)
- **Knight, A. J; Worosz, M. R., and Todd, E. C. D. (2007**). Serving food safety: consumer perceptions of food safety at restaurants. *International Journal of Contemporary Hospitality Management*, 19(6), 476-484.
- **Koenen-Dierick K; Okerman L; De Zutter L; DeGroodt J; Van Hoof J. and Srebmik S. (1995). -** A one-plate microbiological screening test for antibiotic residue testing in kidney tissue and meat - an alternative to the EU 4-plate method. *Food Addit. Contam*., 12 (1), 77-82).
- **Kokkinaki, M; Sahibzada, N., and Golestaneh, N. (2011).** Human induced pluripotent stem-derived retinal pigment epithelium (RPE) cells exhibit ion transport, membrane potential, polarized vascular endothelial growth factor secretion, and gene expression pattern similar to native RPE. *Stem Cells*, 29(5), 825-835.
- **Komolafe, O. O. (2003).** Antibiotic resistance in bacteria-an emerging public health problem. *Malawi Medical Journal*, 15(2), 63-67.
- **Korner, J; Savontaus, E; Chua Jr, S. C; Leibel, R. L., and Wardlaw, S. L. (2001).** Leptin regulation of Agrp and Npy mRNA in the rat hypothalamus. *Journal of neuroendocrinology*, 13(11), 959-966.
- **Korsrud, G.O; Boison, J.O; Papich, M.G; Yates, W.D; MacNeil, J.D; Janzen, E.D;Cohen, R.D; Landry, D.A; Lambert, G. and Yong, M.S., (1993**). Depletion of intramuscularly and subcutaneously injected procaine penicillin G from tissues and plasma of yearling beef steers. *Canadian journal of veterinary research*, 57(4), p.223.
- **Korsrud, G. O; Boison, J. O; Nouws, J. F., and MacNeil, J. D. (1998).** Bacterial inhibition tests used to screen for antimicrobial veterinary drug

residues in slaughtered animals. *Journal of AOAC International*, 81(1), 21-24.

- **Korsrud, G.O; Boison, J.O; Nouws, J.F. and MacNeil, J.D., (1998).** Bacterial inhibition tests used to screen for antimicrobial veterinary drug residues in slaughtered animals. Journal of AOAC International, 81(1), pp.21-24.
- **Küng, H., and Moltmann, J. (1992).** Fundamentalism as an ecumenical challenge (Vol. 3). *SCM Press*.
- **Küng, K; Riond, J.-L; Wolffram, S. and Wanner, M.(1992).** Comparison of an HPLC and Bioassay Method to Determine Antimicrobial Concentrations after Intravenous and Oral Administration of Enrofloxacin in Four Dogs. *Res. Vet. Sci*. 54, 247-248.
- **Kurwijila, L.R; Omore, A; Staal, S; Mdoe, N. S. (2006).** Investigation of the risk of exposure to antimicrobial residues present in marketed milk in Tanzania. *Journal of Food Protection*. 69 (10), 2487–2492.
- **Kurwijila, L R; Mwingira, J; Karimuribo, E; Shirima, G, Lema, B, Royoba R and Kilima, B (2011)** Safety of animal source foods in Tanzania – A situational analysis. *Draft report submitted to ILRI*, Nairobi, Kenya.
- **Lampland, M., and Star, S. L. (Eds.). (2009).** Standards and their stories: How quantifying, classifying, and formalizing practices shape everyday life. *Cornell University Press*.
- **Landers, T. F; Cohen, B; Wittum, T. E., and Larson, E. L. (2012).** A review of antibiotic use in food animals: perspective, policy, and potential. *Public health reports*, 127(1), 4-22.
- **Lara, F. J; del Olmo-Iruela, M;Cruces-Blanco, C; Quesada-Molina, C., and García-Campaña, A. M. (2012).** Advances in the determination of β-

lactam antibiotics by liquid chromatography. *TrAC Trends in Analytical Chemistry*, 38, 52-66.

- **Lassheikki, K; Skogster, H., and Söderström, M. (2016).** Kasvisten Laatujärjestelmien Valintaopas [online]. 1st Ed. Puutarhaliitto-Trädgårdsförbundet ry, Helsinki. Available from Internet: <URL: http://www.pty.fi/fileadmin/user_upload/tiedostot/Julkaisut/Muut_julkaisut/Kasvisten_laatujarjestelmien_valintaopas_2016.pdf>.
- **Latour, B. (1999).** Pandora's hope: essays on the reality of science studies. *Harvard university press*.
- **Lee, H.J; H. Ryu and M.H. Cho. (2001)**. Screening for penicillin plasma residue in cattle by enzyme linked immune-sorbent assay. *Acta Veterinary Brno*.,70: 353-358.
- **Lee, H. J., Lee, M. H. and Han, In K.(2001b).** Application of ELISA for the Detection of Sulfamethazine Residues in Live Lattle. *Asian-Aust. J. Anim.Sci*. 14, 378-381.
- **Lolo, M; S. Pedreira; J. Miranda; B. Va´zquez; C. Franco; A. Cepeda., and C. Fente. (2006)**. Effect of cooking on enrofloxacin residues in chicken tissue. *Food Addit. Contam*. 23:988–993).
- **Lone, K. P. (1997).** Natural sex steroids and their xenobiotic analogs in animal production: growth, carcass quality, pharmacokinetics, metabolism, mode of action, residues, methods, and epidemiology. *Critical reviews in food science and nutrition*, 37(2), 93-209.
- **Lozano, M. C., and Arias, D. C. (2008).** Residuos de fármacos en alimentos de origen animal: panorama actual en Colombia. *Revista Colombiana de Ciencias Pecuarias*, 21(1), 10.

- **Lozano, M. C., and Trujillo, M. (2012).** Chemical residues in animal food products: An issue of public health. In Public Health-Methodology, Environmental and Systems Issues. *InTech*.
- **Lund, B. M., and O'Brien, S. J. (2009).** Microbiological safety of food in hospitals and other healthcare settings. *Journal of Hospital Infection*, 73(2), 109-120.
- **Lusk, A. C; Furth, P. G; Morency, P; Miranda-Moreno, L. F; Willett, W. C., and Dennerlein, J. T. (2011).** Risk of injury for bicycling on cycle tracks versus in the street. *Injury prevention*, 17(2), 131-135.
- **Lusk, J. L; Roosen, J. and Shogren, J. F. (2011).** The Oxford Handbook of the economics of food consumption and policy. Oxford: *University press* ISBN 978-0-19-956944-1.
- **Lynas, L; Currie, D; McCaughey, W. J; McEvoy, J. D., and Kennedy, D. G. (1998).** Contamination of animal feeding stuffs with undeclared antimicrobial additives. *Food Additives and Contaminants*, 15(2), 162-170.
- **Thomas, M.H., (1989).** Simultaneous determination of oxytetracycline, tetracycline, and chlortetracycline in milk by liquid chromatography. *Journal-Association of Official Analytical Chemists*, 72(4), pp.564-567.
- **MacLachlan, D. J., and Bhula, R. (2008**). Estimating the residue transfer of pesticides in animal feedstuffs to livestock tissues, milk and eggs: a review. *Australian Journal of Experimental Agriculture*, 48(5), 589-598.
- **MacNeil, B; Hoffman-Goetz, L; Kendall, A; Houston, M., and Arumugam, Y. (1991).** Lymphocyte proliferation responses after exercise in men: fitness, intensity, and duration effects. *Journal of Applied Physiology*, 70(1), 179-185.

- **Madigan, M. T., and Martinko, J. M. (2006).** Microorganisms and microbiology. *Brock biology of microorganisms*. 11th ed. Upper Saddle River, New Jersey (NJ): Pearson Prentice Hall, 1-20.
- **Magaña-Gómez, J.A. and Calderón de la Barca, A.M.(2009).** Risk assessment of genetically modified crops for nutrition and health. *Nutrition Reviews*, 67(1), pp.1-16.
- **Mahgoub O, Kadim IT, Ann Mothershaw AI, Zadjali SA, Annamalai K.** Use of enzyme-linked immune sorbent assay (ELISA) for detection of antibiotic and anabolic residues in goat and sheep meat. *World Journal of Agricultural Sciences.* (2006); 2:298-302.
- **Marazuela, M. D., and Bogialli, S. (2009).** A review of novel strategies of sample preparation for the determination of antibacterial residues in foodstuffs using liquid chromatography-based analytical methods. *Analytica Chimica Acta*, 645(1-2), 5-17.
- **Mårdén, P. (1995).** Att arbeta med HACCP – hur och varför? (SIK-Rapport nr 617). SIK, Göteborg. ISBN 91-7290-170-5.
- **Maria, C. and T. Mary (2012)**. Chemical Residues in Animal Food Products: An Issue of Public Health Pharmacy Department, Faculty of Sciences and National University of Colombia
- **Mariël, GP.** Microbial screening methods for detection of antibiotic residues in slaughter animals. *Anal BioanalChem*.(2007);395(4): 893–905
- **Martin-Jimenez, T., and Riviere, J. E. (1998).** Population pharmacokinetics in veterinary medicine: potential use for therapeutic drug monitoring and prediction of tissue residues. *Journal of Veterinary Pharmacology and Therapeutics*, 21(3), 167-189.
- **Masztis, P.S. (1984).** Antibiotic Residues Testing in a Beef Slaughterhouse. *Can. Vet. J.* 25: 329-330.

- **Matz, C; Bergfeld, T; Rice, S. A., and Kjelleberg, S. (2004).** Microcolonies, quorum sensing and cytotoxicity determine the survival of Pseudomonas aeruginosa biofilms exposed to protozoan grazing. *Environmental microbiology*, 6(3), 218-226. May 2012].
- **Mayes, T., and Mortimore, S. (Eds.). (2001).** Making the most of HACCP: Learning from others' experience. *Wood head Publishing*.
- **McCalla, D. R. (1983).** Mutagenicity of nitrofuran derivatives. *Environmental mutagenesis*, 5(5), 745-765.
- **McCaughey, W. J; Elliott, C. T., and Crooks, S. R. H. (1990).** Determination of sulphadimidine in animal feedstuffs by an enzyme-linked immunoassay. *Food Additives and Contaminants*, 7(2), 259-264.
- **McConville ML; Dijkstra JW; Stamm JM; Van Saene JJ; Nouws JF (1995)** Eéects of sarafloxacin hydrochloride on human enteric bacteria under simulated human gut conditions. *Vet Q* 17: 1-5.
- **McCracken, J. T; Smalley, S. L; McGough, J. J; Crawford, L; Del'Homme, M; Cantor, R. M., and Nelson, S. F. (2000).** Evidence for linkage of a tandem duplication polymorphism upstream of the dopamine D4 receptor gene (DRD4) with attention deficit hyperactivity disorder (ADHD). *Molecular psychiatry*, 5(5), 531.
- **McEvoy JD G. (2002).** Contamination of animal feedstuffs as a cause of residues in food. A review of regulatory aspect, incidence and control. *Anal Chim Acta*.473: 3–26.
- **McEvoy, G. K. (1994).** AHFS drug information. *Oncology Issues*, 9(5), 12-13.
- **McEwen, B. S. (2006).** Protective and damaging effects of stress mediators: central role of the brain. *Dialogues in clinical neuroscience*, 8(4), 367.

- **McEwen, S. A., and Fedorka-Cray, P. J. (2002).** Antimicrobial use and resistance in animals. *Clinical Infectious Diseases*, 34(Supplement_3), S93-S106.
- **McGrane, M. (2000).** Analysis of antibiotic drug residues in biological matrices, after evaluation of various extraction methodologies and determination procedures (Doctoral dissertation, Dublin City University).
- **McSwane, D. R; Rue, N. R; Linton, R; Willliams, A. G; McSwane, D., and Rue, N. (2000).** The Essentials of Food Safety and Sanitation (3rd. meat and meat products. The EFSA *Journal, 510: 1-62.Med*. 20: 161-178.medical setting. Clin. Chim. Acta 315:125-135.medicated feeds. Title 21, Part 225.
- **Medina, R; Wing, S. S., and Goldberg, A. L. (1995).** Increase in levels of polyubiquitin and proteasome mRNA in skeletal muscle during starvation and denervation atrophy. *Biochemical Journal*, 307(3), 631-637.
- **Mellon, M.G; Benbrook, C. and Benbrook, K.L., (2001).** Hogging it: *estimates of antimicrobial abuse in livestock*. Union of Concerned Scientists.
- **Meng, M. and Xi, R. (2011).** *Anal. Lett*., 44: 2543-2558.
- **Mensah, P; Yeboah-Manu, D; Owusu-Darko, K., and Ablordey, A. (2002).** Street foods in Accra, Ghana: how safe are they? *Bulletin of the World Health Organization*, 80, 546-554.
- **Mensah, L. D., and Julien, D. (2011).** Implementation of food safety management systems in the UK. *Food Control*, 22(8), 1216-1225.
- **Mensah, S. E; Koudande, O. D;, P; Laurentie, M; Mensah, G. A., and Abiola, F. A. (2014).** Antimicrobial residues in foods of animal origin in Africa: public health risks. *Rev. Sci. Tech*, 33, 987-996.
- **Mesgari Abbasi M; Nemati M; Babaei H; Ansarin M; Nourdadgar A. (2012)**. Solid-Phase Extraction and Simultaneous Determination of

Tetracycline Residues in Edible Cattle Tissues Using an HPLC-FL Method. *IJPR*.11: 781-787.

- **Meyer, M; Friederici, A. D., and Von Cramon, D. Y. (2000).** Neurocognition of auditory sentence comprehension: event related fMRI reveals sensitivity to syntactic violations and task demands. *Cognitive Brain Research*, 9(1), 19-33.
- **Miljöstyrningsrådet. (2007).** Certifierings- och kvalitetssystem inom livsmedelskedjan.
- **Mitchell, J.M; Griffiths, M.W; McEwen, S.A; McNab, W.B. and Yee, A.J., (1998)**. Antimicrobial drug residues in milk and meat: causes, concerns, prevalence, regulations, tests, and test performance. *Journal of food protection*, 61(6), pp.742-756.
- **Mitchell, A. A. (2000).** Special considerations in studies of drug-induced birth defects. *Pharmacoepidemiology*, 749-763.
- **Moats, W. A. (1999).** The effect of processing on veterinary residues in foods. In Impact of processing on Food Safety (pp. 233-241). Springer, Boston, MA.modified crops for nutrition and health. *Nutrition Reviews*, 67: 1-16
- **Mohamed Bashir Wahab Alla; Twfig Eltigani Mohamed., and Atif Elamin Abdelgadir (2011).** Detection of Antibiotics Residues in beef in Ghanawa Slaughter house, Khartoum state, Sudan. *U of K. J. Vet. Med. and Anim. Prod*. Vol. 2, No. 1, 2011(71-88).
- **Albayoumi, M. A. (2015).** Detection of Antibiotic Residues in Broiler Chickens in Gaza Strip. *Detection of Antibiotic Residues in Broiler Chickens in Gaza Strip.*

- **Mohammed-Alfa, M and Tano-Debrah, K (2011)** Safety of animal source foods in Ghana – A situational analysis. *Draft report submitted to ILRI*, Nairobi, Kenya.
- **Nada Khalifa Mohamed Monsour (1996).** Safety of meat and fish (Sahat el lihom wa elusmack) part one. 1th ed. University of Omer Elmokhtar, Leibya. Pp 294-297.
- **National Research Council (NRC) (1991)** the use of drugs in food animal benefits and risks. *The National academies Press* 253: 284.
- **National Research Council (US).** Committee on the Comparative Costs of Rock Salt, and Calcium Magnesium Acetate (CMA) for Highway Deicing. (1991). Highway deicing: comparing salt and calcium magnesium acetate (No. 235). Transportation Research Board.
- **Naveh, E., and Marcus, A. (2005).** Achieving competitive advantage through implementing a replicable management standard: Installing and using ISO 9000. *Journal of Operations Management*, 24(1), 1-26.
- **NaVrátiloVá, P.,(2008).** Screening methods used for the detection of veterinary drug residues in raw cow milk–a review. *Czech J Food Sci*, 26(6), pp.393-401.
- **Nicholls, T. J; McLean, G. D; Blackman, N. L., and Stephens, I. B. (1994**). Food safety and residues in Australian agricultural produce. *Australian veterinary journal*, 71(12), 393-396.
- **Nisha, A. R. (2008).** Antibiotic residues-a global health hazard. *Veterinary world*, 1(12), 375.
- **Nollet, C. (1992).** Lean I. Gabszewicz, Paolo Garella and. *Market Strategy and Structure*, 168.
- **Nollet, J., and Haywood-Farmer, J. (1992**). Services et management. *De Boeck Université*. De Boeck Université.

- **Nonga, H. E; M. Mariki; E. D. Karimuribo and R. H. Mdegela (2009**). Assessment of Antimicrobial Usage and Antimicrobial Residues in Broiler Chickens in Morogoro Municipality, Tanzania. *Pakistan Journal of Nutrition*, 8(3):203-207.
- **Nonga, H. E; Sungura, K. H., andNgowi, H. A. (2013).** Assessment of veterinary drug use and determination of antimicrobial residues in broiler chicken meat in Urban district, Zanzibar, Tanzania.
- **Norcross, M. A., and Post, A. R. (1990).** New food safety initiatives in the Food Safety and Inspection Service, US Department of Agriculture. *Journal of animal science*, 68(3), 863-869.
- **Novais, A; Comas, I; Baquero, F; Canton, R; Coque, T. M; Moya A; Gonzalez-Candelas F and Galan J. C. (2001).** Evolutionary trajectories of beta-lactamase CTX-M-1 cluster enzymes: predicting antibiotic resistance. *PLoS Pathogens*. 6(1), e1000735.
- **Novotny MJ:** *Clinical Pharmacology*: Principles of Therapeutics. In: Antimicrobial Therapy in veterinary y Medicine. eds *Prescott, J.F., Baggot,* R.D. and Walker, R.D. 3rd Edition; *Iowa State University Press USA*; (2001): 63pp.
- **NRC, U. (1999).** Arsenic in drinking water. *US National Research Council*.
- **Oakland, J. S. (2014).** Total quality management and operational excellence: text with cases. Routledge.
- **O'Connell, J. (1993).** Metrology: The creation of universality by the circulation of particulars. *Social studies of science*, 23(1), 129-173.
- **Oka, A; Belliveau, M. J; Rosenberg, P. A., and Volpe, J. J. (1993).** Vulnerability of oligodendroglia to glutamate: pharmacology, mechanisms, and prevention. *Journal of Neuroscience,* 13(4), 1441-1453.

- **Oka, H; Ito, Y., and Matsumoto, H. (2000).** Chromatographic analysis of tetracycline antibiotics in foods. *Journal of Chromatography* A, 882(1-2), 109-133.
- **Okerman L; Van Hoof J; Debeuckelaere W. (1997).** Evaluation of the European four-plate test as a tool for screening antibiotic residues in meat samples from retail outlets. *Journal of AOAC International*. 81: 51-56.
- **Okerman, L; De Wasch, K; Van Hoof, J. and Smedts, W. (2003**). Simultaneous Determination of Different Antibiotic Residues in Bovine and in Porcine Kidneys by Solid-phase Fluorescence Immunoassay. *J. AOAC*.
- **Okerman, L; S. Croubels; M. Cherlet; K. De Wasch; P. De Backer and J. Van Hoof. (2004).** Evaluation and establishing the performance of different screening tests for tetracycline residues in animal tissues. *Food Addit*. Contam., 21:145–153.
- **Okerman, L; J. Van Hende, and L. De Zutter. (2007)**. Stability of frozen stock solutions of beta-lactam antibiotics, cephalosporins, tetracyclines and quinolones used in antibiotic residue screening and antibiotic susceptibility testing. *Anal. Chim*. Acta 586:284–288.
- **Oliveira, M. R; Batista, C. R. V., and Aidoo, K. E. (2001).** Application of hazard analysis critical control points system to enteral tube feeding in hospital. *Journal of human nutrition and dietetics*, 14(5), 397-403.
- **Opinion Research Corporation. (1990).** Food labeling and nutrition: What Americans want-Summary of findings.
- **Osborn, L; Albright, K; Southard, K., and German, M. A. (1997).** An Investigation of Hazard Analysis Critical Control Point Programs (HACCP) in Hospital Foodservice Facilities: A Nationwide Survey. *Journal of the American Dietetic Association*, 97(9), A80.

- **Ozbay, G; Babu, B. K., and Chen, G. (2013).** Prevalence of veterinary drug residues and heavy metals in catfish nuggets. *J Food Process Technol S11*-005. doi, 10, 2157-7110.
- **Page, R. C. (1991).** The role of inflammatory mediators in the pathogenesis of periodontal disease. *Journal of periodontal research*, 26(3), 230-242.
- **Papich, M. G., and Riviere, J. E. (2001).** Fluoroquinolone antimicrobial drugs. *Veterinary pharmacology and therapeutics*, 9.
- **Paul, S. (1997)**. Contaminated food of animal origin: hazards and risk management.
- **Peippo, P; Lövgren, T., and Tuomola, M. (2005).** Rapid screening of narasin residues in poultry plasma by time-resolved fluoroimmunoassay. *Analytica chimica acta*, 529(1-2), 27-31.
- **Peters, J. P; Shen, R. Y. W., and Chester, S. T. (1990).** Propionic acid disappearance from the foregut and small intestine of the beef steer. *Journal of animal science*, 68(11), 3905-3913.
- **Petz, M; Lebensmittelchem.-Gerichtl.-Chem., (1986), 40, 62-66.**
- **Picó, Y., and Barceló, D. (2008).** The expanding role of LC-MS in analyzing metabolites and degradation products of food contaminants. *TrAC Trends in Analytical Chemistry*, 27(10), 821-835.
- **Piddock, l. J. (1996)**. Does the use of antimicrobial agents in veterinary medicine and animal husbandry select antibiotic-resistant bacteria that infect man and compromise antimicrobial chemotherapy? *Journal of Antimicrobial Chemotherapy*, 38(1), 1-3.
- **Pikkemaat, M. G. (2009).** Microbial screening methods for detection of antibiotic residues in slaughter animals. *Analytical and bioanalytical chemistry*, 395(4), 893-905.

- **Pikkemaat, M. G; Rapallini, M. L; Oostra-van Dijk, S., and Elferink, J. A. (2009).** Comparison of three microbial screening methods for antibiotics using routine monitoring samples. *Analytica chimica acta*, 637(1-2), 298-304.
- **Pikkemaat, MG; OostravanDijk, S; Schouten, J; Rapallini, M; Kortenh oeven, L and Van, Egmond HJ. (2009a)**. Nouws Antibiotic Test: validation of a post-screening method for antibiotic residues in kidney. *Food Contr*, 20: 771–777.
- **Pikkemaat, MG; Rapallini, MLBA; Oostra-van; Dijk, S and Elferink, JWA. (2009b).** Comparison of three microbial screening methods for antibiotics using routine monitoring samples. *Anal Chim Acta*, 637: 298–304.
- **Pikkemaat, M. G; Rapallini, M. L; Zuidema, T; Elferink, J. A; Oostra-Van Dijk, S., and Driessen-Van Lankveld, W. D. (2011).** Screening methods for the detection of antibiotic residues in slaughter animals: comparison of the European Union Four-Plate Test, the Nouws Antibiotic Test and the Premi® Test (applied to muscle and kidney). *Food Additives and Contaminants*: Part A, 28(1), 26-34.
- **Pillay, V., and Muliyil, V. (2005).** ISO 22000 Food Safety Management Systems–The One Universal Food Safety Management System Standard That Works Across All Others. *SGS Systems and Certifications Services,* Surrey.
- **Popelka, J. C; Terryn, N., and Higgins, T. J. V. (2004).** Gene technology for grain legumes: can it contribute to the food challenge in developing countries? Plant Science, 167(2), 195-206.*Pract Res Clin Endocrinol Metab*. 14:147-165.

- **Prescott, J. F. (2008).** Antimicrobial use in food and companion animals. *Animal Health Research Reviews*, 9(2), 127-133.
- **Prescott, J. F. (2000e).** Aminoglycosides and aminocyclitols. In:**Prescott, J. F., Baggot, J. D. and Walker, R. D. (eds.)** Antimicrobial Therapy in Veterinary Medicine, 3rd ed. Ames, Iowa, USA, pp. 191-228.prevention: a quality assurance protocol. *J Ame Vet Assoc* 2: 1-24.
- **Prescott, J. F; Baggot, J. D. and Walker, R. D. (eds.)** Antimicrobial Therapy in Veterinary Medicine,3rd ed. *Ames, Iowa*, USA, pp. 744-759.
- **Production Fed-eration (NMPF) (1991)** Milk and beef residueproduction: growth, carcass quality, pharmacokinetics, metabolism, mode of proteins in meat products: A review.
- **Ramirez, R. R., and De La Cruz, G. P. (2003).** The Hispanic Population in the United States: March 2002. Population Characteristics. *Current Population Reports*.
- **Ramatla, T; Ngoma, L; Adetunji, M., and Mwanza, M. (2017).** Evaluation of Antibiotic Residues in Raw Meat Using Different Analytical Methods. *Antibiotics*, 6(4), 34.
- **Ramirez, S; Hild, T. G; Rudolph, C. N; Sty, J. R; Kehl, S. C; Havens, P., and Chusid, M. J. (2003).** Increased diagnosis of Lemierre syndrome and other Fusobacterium necrophorum infections at a Children's Hospital. *Pediatrics*, 112(5), e380-e380.
- **Randecker, V. W; Reagan, J. A; Engel, R. E; Soderberg, D. L., and Mcneal, J. E. (1987).** Serum and urine as predictors of sulfamethazine levels in swine muscle, liver and kidney. *Journal of food protection*, 50(2), 115-122.
- **Reeves, P.T. (2005).** The safety assessment of chemical residues in animal-derived foods. *Aust.Vet. J.* 83:151-153.36

- **Reeves, P.T. (2007).** Residues of veterinary drugs at injection sites. *J. Vet. Pharmacol*. Ther. 30:1-17.
- **Reig, M., and Toldrá, F. (2008).** Veterinary drug residues in meat: Concerns and rapid methods for detection. *Meat science*, 78(1-2), 60-67.
- **Reig, M; Batlle, N; Navarro, J. L., and Toldrá, F. (2005a**). A modified HPLC method for the detection of 6-methyl-2-thiouracil in cattle urine. In Proceedings of the international congress in meat science and technology, *Baltimore, MD* (pp. 7-12).
- **Resurreccion AVA, Galvez FCF (1999)** Will consumers buy irradiated beef? Food Technol 53(3):52–55
- **Richards, D. A; Obrenovitch, T. P; Johonson-Mora, A; Islekel, S; Symon, L., and Curzon, G. (1993).** Effect of global ischaemia, under simulated penumbral conditions, on brain monoamine neurochemistry and subsequent neurological and histological deficits. *Journal of neurochemistry*, 61(5), 1801-1807.
- **Richards, J; Parr, E., and Riseborough, P. (1993).** Hospital food hygiene: the application of Hazard Analysis Critical Control Points to conventional hospital catering. *Journal of Hospital Infection*, 24(4), 273-282.
- **Riedl, M. A., and Casillas, A. M. (2003).** Adverse drug reactions: types and treatment options. *American family physician*, 68(9), 1781-1790.
- **Rigamonti, A; Scandroglio, M; Minicucci, F; Magrin, S; Carozzo, A., and Casati, A. (2005).** A clinical evaluation of near-infrared cerebral oximetry in the awake patient to monitor cerebral perfusion during carotid endarterectomy. *Journal of clinical anesthesia*, 17(6), 426-430.
- **Riswadkar, A.V. (2000).** An introduction to HACCP, the hazard analysis and critical control point system for food processors. *Profes. Safety*. 45: 33-36.

- **Rivier, L. (2000).** Techniques for analytical testing of unconventional samples. *Best Practice & Research Clinical Endocrinology & Metabolism*, 14(1), 147-165.
- **Riviere J.E; Sundlof S.F:** Chemical Residue in Tissues of Food Animals. In: *Veterinary Pharmacology and Therapeutics*. Edd Adams HR: 8th Edition; Blackwell Publishing Professional Iowa; (2001): pp1166-1174. (S).
- **Riviere JE; Craigmill AL; Sundlof SF (1991)** Handbook of comparative pharmacokinetics and residues of veterinary antimicrobials. Boca Raton, *FL (Ed) CRC press, Inc*, Florida, USA
- **Riviere, J. E. (1991).** Pharmacologic principles of residue avoidance for veterinary practitioners. *Journal of the American Veterinary Medical Association*, 198(5), 809.
- **Riviere, J. E. and Spoo, J. W. (1995).**Tetracycline Antibiotics. In: *Adams, R. H. (ed.) Veterinary Pharmacology and Therapeutic.,* 7th ed. Iowa State University press, Ames, Iowa, USA, pp.784-796.
- **Riviere, J. E., and Williams, P. L. (1999).** Noncompartmental models. In Comparative pharmacokinetics: *principles, techniques, and applications* (pp. 148-167). Iowa State Press, USA.
- **Robertson, D. L., and Joyce, G. F. (1990).** Selection in vitro of an RNA enzyme that specifically cleaves single-stranded DNA. *Nature,* 344(6265), 467.
- **Roberts, K.E., Randall, H.T., Farr, H.W., Kidwell, A.P., McNeer, G.P. and Pack, G.T. (1954).** Cardiovascular and blood volume alterations resulting from intrajejunal administration of hypertonic solutions to gastrectomized patients: the relationship of these changes to the dumping syndrome. *Annals of surgery,* 140(5), p.631.

- **Rocourt J; Moy G; Vierk K; Schlundt J. (2003)**. The Present State of Foodborne disease in OECDCountries. World Health Organization, *Food Safety Department*, (ISBN 92 4 159109 9). pp. 8-9.
- **Rodriguez, M; Valero, A; Carrasco, E; Pérez-Rodríguez, F; Posada, G. D., and Zurera, G. (2011).** Hygienic conditions and microbiological status of chilled Ready-To-Eat products served in Southern Spanish hospitals. *Food Control*, 22(6), 874-882.
- **Rodriguez, M; Valero, A; Carrasco, E; Pérez-Rodríguez, F; Posada, G. D., and Zurera, G. (2011).** Hygienic conditions and microbiological status of chilled Ready-To-Eat products served in Southern Spanish hospitals. *Food Control*, 22(6), 874-882.
- **Rokka, M., and Peltonen, K. (2006):** Simultaneous determination of four coccidiostats in eggs and broiler meat: Validation of an LC-MS/MS method. *Food Additives and Contaminants*, 23, 470–478.
- **Rokka, M; Eerola, S; Perttilä, U; Rossow, L; Venäläinen, E; Valkonen, E., and Peltonen, K. (2005).** The residue levels of narasin in eggs of laying hens fed with unmedicated and medicated feed. *Molecular nutrition and food research*, 49(1), 38-42.
- **Ropkins, K., and Beck, A. J. (2000).** Evaluation of worldwide approaches to the use of HACCP to control food safety. *Trends in Food Science and Technology*, 11(1), 10-21.
- **Rose, M. D; Shearer, G., and Farrington, W. H. H. (1997).** The effect of cooking on veterinary drug residues in food; 5. Oxfendazole. *Food Additives and Contaminants*, 14(1), 15-26.
- **Ruiter, A. (1985).** Contaminants in meat and meat products. Development in Meat Science-3, 185-220.

- **Rusjan, B., and Alič, M. (2010).** Capitalising on ISO 9001 benefits for strategic results. *International Journal of Quality and Reliability Management*, 27(7), 756-778.
- **Russell, B. (2004).** Power: A new social analysis. Routledge.2004.
- **Sai, N.I; Chen,Y; Liu, N; Yu, G; Su, P; Feng, Y; Zhou, Z; Liu, X; Zhou, H; Gao, Z. and Ning, B.A. (2010).**A sensitive immunoassay based on direct hapten coated format and biotin–streptavidin system for the detection of chloramphenicol. *Talanta*, 82: 1113-1121.
- **Samanidou, V., and Nisyriou, S. (2008).** Multi-residue methods for confirmatory determination of antibiotics in milk. *Journal of separation science*, 31(11), 2068-2090.
- **Samarajeewa, U; Wei, C. I; Huang, T. S., and Marshall, M. R. (1991).** Application of immunoassay in the food industry. *Critical Reviews in Food Science and Nutrition*, 29(6), 403-434.
- **Sampaio, P; Saraiva, P., and Guimarães Rodrigues, A. (2009).** ISO 9001 certification research: questions, answers and approaches. *International Journal of Quality and Reliability Management*, 26(1), 38-58.
- **Sande, M. A., and Mandell, G. L. (1980).** Chemotherapy of microbial diseases. The pharmacological basis of therapeutics, 1080-1248.
- **Sanders, P. (2007).** The Contact Work Primer. A concise, accesible and comprehensive introduction to Pre-Therapy and the work of Garry Prouty.
- **Sawant, A. A; Sordillo, L. M., and Jayarao, B. M. (2005).** A survey on antibiotic usage in dairy herds in Pennsylvania. *Journal of Dairy Science*, 88(8), 2991-2999.
- **Scallan E; Griffin PM; Angulo FJ; Tauxe RV; Hoekstra RM;** Foodborne illness acquired in the United States—Unspecified agents. *Emerg Infect Dis* (2011a);17:16–22.

- **Scallan E; Hoekstra RM; Angulo FJ; Tauxe RV; Widdowson MA; Roy SL; Jones JL; Griffin PM.** Foodborne illness acquired in the United States—Major pathogens. *Emerg Infect Dis* (2011b);17:7–15.
- **Scheidy S.F. (1951).** – Antibiotic therapy in veterinarymedicine. *JAVMA*, 118 (889), 213–220.
- **Schepkins, E; Duchatel, V. P., and Vindevogel, H. (1985).** Traitement de l'ascaridiose et de la capillariose du pigeon par l'ivermectine. *Ann. Med. Vet*., 129, 475-485.
- **Schindler, P; Koenig, W; Chatterjee, S., and Ganguli, B., J.** *Antibiotic.*, (1986), 39, 53-59.
- **Schlegel, H. B. (2003).** Exploring potential energy surfaces for chemical reactions: an overview of some practical methods. *Journal of computational chemistry*, 24(12), 1514-1527.
- **Schneider, M. J; Reyes-Herrera, I., and Donoghue, D. J. (2007**). Evaluation of serum as a potential matrix for multiresidue determination of fluoroquinolone antibiotics in chicken using liquid chromatography-fluorescence-mass spectrometryn. *Journal of AOAC International*, 90(6), 1716-1723.shahi.
- **Schneider, M.J. and Lehotay, S.J. (2008).** A comparison of the FAST, Premi® and KIS™ tests for screening antibiotic residues in beef kidney juice and serum. *Analytical and bioanalytical chemistry*, 390(7), pp.1775-1779.
- **Schneider, M. J; Mastovska, K; Lehotay, S. J; Lightfield, A. R; Kinsella, B., and Shultz, C. E. (2009).** Comparison of screening methods for antibiotics in beef kidney juice and serum. *Analytica chimica acta*, 637(1-2), 290-297.

- **Schwarz, J.M., Cooper, D.N., Schuelke, M. and Seelow, D. (2014).** MutationTaster2: mutation prediction for the deep-sequencing age. *Nature methods*, 11(4), p.361.
- **Schumacher, Z; C. Bourquin and U. Heininger. (2010)**. Surveillance for adverse events following immunization (AEFI) in Switzerland Vaccine,28(24): 4059-4064.
- **Scippo, M. L; Degand, G; Duyckaerts, A; Maghuin-Rogister, G., and Delahaut, P. (1994).** Control of the illegal administration of natural steroid hormones in the plasma of bulls and heifers. *Analyst*, 119(12), 2639-2644.
- **Selimoglu, E. (2007).** Aminoglycoside-induced ototoxicity. *Current pharmaceutical design*, 13(1), 119-126.
- **Seri, H. I. (2013).** Introduction to veterinary drug residues: hazards and risks. In Workshop of veterinary drug residues in food derived from animal (pp. 26-27).
- **Settepani, J. A. (1984).** The hazard of using chloramphenicol in food animals. *Journal of the American Veterinary Medical Association*, 184(8), 930-931.
- **Shahid, M. A; M. Siddique; S. U. Rehman; S. Hameed and A. Hussain (2007).** Evaluation of a Microbiological Growth Inhibition Assay as a Screening Test for the Presence of Antibiotic Residues in Poultry Meat. *American journal of food technology*, 2(5):457-461.
- **Shaikh, B., and Allen, E. H. (1985).** Overview of physical-chemical methods for determining aminoglycoside antibiotics in tissues and fluids of food-producing animals. *Journal-Association of Official Analytical Chemists*, 68(5), 1007-1013.
- **Shanaghy, N; Murphy, F., and Kennedy, K. (1993**). Improvements in the microbiological quality of food samples from a hospital cook-chill system

since the introduction of HACCP. *Journal of Hospital Infection*, 23(4), 305-314.

- **Shankar, V; Venkatesh, A; Hofacker, C., and Naik, P. (2010).** Mobile marketing in the retailing environment: current insights and future research avenues. *Journal of interactive marketing*, 24(2), 111-120.
- **Shao, Y. Y; Rice, P. D., and Bobbitt, D. R. (1989).** Improvements in the qualitative and quantitative study of erythromycins using laser-based polarimetric detection. *Analytica chimica acta*, 221, 239-247.
- **Sharfstein, J. M. (2010).** Statement of Joshua M. Sharfstein, MD, Principal Deputy Commissioner. Food and Drug Administration, Department of Health and Human Services, before the Sub-Committee on Health, Committee on Energy and Commerce, US House of Representatives. *FDA Press Release*, 10.
- **Shih, K.M. and Wang, W.K. (2011).** Factors influencing HACCP implementation in Taiwanese public hospital kitchens. *Food Control*, 22(3-4), pp.496-500.
- **Silfrany, R. O; Caba, R. E; de Los Santos, F. S., and Hanning, I. (2013).** Detection of quinolones in poultry meat obtained from retail centers in Santiago Province, the Dominican Republic. *Journal of food protection*, 76(2), 352-354.
- **Sinclair, U. (2014).** The Jungle:(1906). CreateSpace Independent Publishing Platform.
- **Sivaraman, A. (2007).** Melamine in pet food, wheat gluten from China: FDA. Reuters.
- **Slana, M., and Dolenc, M. S. (2013).** Environmental risk assessment of antimicrobials applied in veterinary medicine—a field study and laboratory approach. *Environmental toxicology and pharmacology*, 35(1), 131-141.

- **Slaton, A., and Abbate, J. (2001).** The hidden lives of standards: technical prescriptions and the transformation of work in America. *Technologies of power*, 95-144.
- **Slatore, C. G., and Tilles, S. A. (2004).** Sulfonamide hypersensitivity. *Immunology and Allergy Clinics*, 24(3), 477-490.
- **Souness, R. (2000).** HACCP in Australian food control. *Food Control*, 11, (5), 353-357.
- **Spencer, R.S., (1950).** Flow of linear amorphous polymers. *Journal of Polymer Science*, 5(5), pp.591-608.
- **Srikandakumar, A; Johnson, E. H; Nsanzi, H., and Al-Abri, K. S. (2004).** Microbes and anti-microbial substances in pasteurized milk sold in Oman. *International journal of food properties*, 7(3), 615-627.
- **Stanier R. Y; Doudero M., and Adelberg E. A. (1968)** *General Microbiology*. MacMillan, London.
- **Stahl, G. K., and Voigt, A. (2008).** Do cultural differences matter in mergers and acquisitions? A tentative model and examination. *Organization science*, 19(1), 160-176.
- **Stawinski J; Szafranski K; Vullo D. and Supuran C. T. (2013).** Carbonic anhydrase inhibitors. Synthesis of heterocyclic 4-substituted pyridine3-sulfonamide derivatives and their inhibition of the human cytosolic isozymes I and II and transmembrane tumor- associated isozymes IX and XII. *Eur. J. Med. Chem.* 69:701-710.
- **Stead, D. A. (2000).** Current methodologies for the analysis of aminoglycosides. *Journal of Chromatography B*: Biomedical Sciences and Applications, 747(1-2), 69-93.
- **Steinmetz, K. A., and Potter, J. D. (1991).** Vegetables, fruit, and cancer. I. *Epidemiology. Cancer Causes and Control*, 2(5), 325-357.

- **Stigzelius, I. (2009).** Making standards work (No. 2140). Swedish University of Agricultural Sciences, Department of Economics.
- **Stolker, A. A. M., and Brinkman, U. T. (2005).** Analytical strategies for residue analysis of veterinary drugs and growth-promoting agents in food-producing animals—a review. *Journal of Chromatography* A, 1067(1-2), 15-53.
- **Stoloff, L. (1979).** Mycotoxin residues in edible animal tissues. Proc. Symp. Interactions of Mycotoxins in Animal Production, Nutritional Academy of Sciences, Washington,
- **Suhren, G; Reichmuth, J., and Walte, H. G. (1996).** Detection of beta-lactam antibiotics in milk by the Penzym-test. Milchwissenschaft (Germany).
- **Sundlof SF; Fernandez AH; Paige JC:** Antibiotic Residues in Food Producing Animals. In: Antimicrobial Therapy in Veterinary Medicine. eds Prescott JF, Baggot RD, Walker RD: 3rd Edition; (2000): *Iowa State University Press,* USA. Pp744-759. (s)
- **Surak, J. G. (2003).** HACCP and ISO development of a food safety management standard. Department of Science and Human Nutrition, 224.
- **Surak, K. (200**6). 'Ethnic practices' in translation: Tea in Japan and the US. *Ethnic and racial studies*, 29(5), 828-855.
- **Surak, J. G. (2007).** A recipe for safe food: ISO 22000 and HACCP. *Quality Progress*, 40(10), 21.
- **Swann, M. M; Baxter, K. L., and Field, H. I. (1969).** Report of the joint committee on the use of antibiotics in animal husbandry and veterinary medicine. Published by HMSO. (1969).
- **Swarm, R. L; Roberts, G. K. S; Levy, A. C., and Hines, L. R. (1973).** Observations on the thyroid gland in rats following the administration of

sulfamethoxazole and trimethoprim. *Toxicology and applied pharmacology*, 24(3), 351-363.

- **Taber, S. S., and Pasko, D. A. (2008).** The epidemiology of drug-induced disorders: the kidney. *Expert opinion on drug safety*, 7(6), 679-690.
- **Tajik , H; Malekinejad, H; Razavi-Rouhani, S.M; Pajouhi ,M.R; Mahmoudi, R; A. Haghnazari, A**. Chloramphenicol residues in chicken liver, kidney and muscle: A comparison among the antibacterial residues monitoring methods of Four Plate Test, ELISA and HPLC . *Food and Chemical Toxicology*. **(1998);** 48 2464–2468.
- **Tajick, M.A. and Shohreh, B. (2006)**. Detection of Antibiotics Residue in Chicken Meat Using TLC. *International Journal of Poultry Science*. 5 (7), 611–612.
- **Tajik, H; Malekinejad, H; Razavi-Rouhani, S. M; Pajouhi, M. R; Mahmoudi, R., and Haghnazari, A. (2010).** Chloramphenicol residues in chicken liver, kidney and muscle: A comparison among the antibacterial residues monitoring methods of Four Plate Test, ELISA and HPLC. *Food and chemical toxicology*, 48(8-9), 2464-2468.
- **Takizawa, T. K; Hashimoto, N; Itoh, S. Yamashita and K. Owen. (1999a)**. A comparative study of the repeat dose toxicity of grepafloxacin and a number of other fluoroquinolones in rats. *Hum. Exp. Toxicol*. 18:38-45.
- **Takizawa, T; K. Hashimoto; K. Minami, S; Yamashita and K. Owen. 1999b.** The comparative arthropathy of fluoroquinolones in dogs. *Hum Exp. Toxicol*. 18:392-399.
- **Talaro K. P. and Chess B. (2008).** *Foundations in microbiology*. 8th Ed. McGraw Hill, New York.

- **Tang, H.P.O; Ho, C. and Lai, S.S.L., .(2006):** High-throughput screening for multi-class veterinary drug residues in animal muscle using liquid chromatography/tandem mass spectrometry with on-line solid-phase extraction .*Rapid Communications in Mass Spectrometry*, 20,2565–2572.
- **Tang, J. S., and Gillevet, P. M. (2003).** Reclassification of ATCC 9341 from Micrococcus luteus to Kocuria rhizophila. *International journal of systematic and evolutionary microbiology*, 53(4), 995-997.
- **Thevis, M; Opfermann, G., and Schänzer, W. (2003).** Liquid chromatography/ electrospray ionization tandem mass spectrometric screening and confirmation methods for β2- agonists in human or equine urine. *Journal of Mass Spectrometry*, 38(11), 1197-1206.
- **Thrusfield, M. (2007)** Veterinary Epidemiology. 3rd ed., Ch. 13. *Black Well Science Ltd*., United Kingdom. p228-246.
- **Tinkelman, D. G., and Bock, S. A. (1984).** Anaphylaxis presumed to be caused by beef containing streptomycin. *Annals of allergy*, 53(3), 243-244.
- **Tokuç, B; Ekuklu, G; Berberoğlu, U; Bilge, E., and Dedeler, H. (2009).** Knowledge, attitudes and self-reported practices of food service staff regarding food hygiene in Edirne, *Turkey*. *Food Control*, 20(6), 565-568.
- **Toldrá, F. and Reig, M. (2006).** Methods for rapid detection of chemical and veterinary drug residues in animal foods. *Trends in Food Science and Technology*, 17(9), 482-489.
- **Tollefson, L. and Miller, M.A., (2000).** Antibiotic use in food animals: controlling the human health impact. *Journal of AOAC international*, 83(2), pp.245-254.
- **Tollefson, L., and Flynn, W. T. (2002**). Impact of antimicrobial resistance on regulatory policies in veterinary medicine: status report. *AAPS PharmSci*, 4(4), 150-159.

- **Tollefson L.** Developing new regulatory approaches to antimicrobial safety. *J Vet Med B Infect Dis Vet Public Health*. (2004); 51:415–418. doi: 10.1111/j.1439-0450.2004.00781.x.
- **Tomlinson, E; Fu, L; John, L; Hultgren, B; Huang, X; Renz, M., and Stewart, T. A. (2002**). Transgenic mice expressing human fibroblast growth factor-19 display increased metabolic rate and decreased adiposity. *Endocrinology*, 143(5), 1741-1747.
- **Toutain PL; Ferran A; Bousquet-Me´lou A (2010)** Species Di؛erences in Pharmacokinetics and Pharmacodynamics. In: Cunningham F, Elliot J, Lees P (Eds) Comparative and Veterinary Pharmacology: *Handbook of Experimental Pharmacology*, Springer-Verlag Berlin Heidelberg,pp. 199 Toxicol. Pathol. 23:209-216.
- **Triune T. and Upson D. (1989).** - Factors affecting the accuracy of the live animal swab test for detecting urine Oxytetracycline and predicting Oxytetracycline residues in calves *J. Am. vet. med. Assoc*., 194 (7), 918-921).
- **Trivedi, M. S. (2012).** Detection of antibiotics residues in muscle, liver and kidney of chicken (Doctoral dissertation, Nanaji Deshmukh Veterinary Science University, Jabalpur.
- **Turnidge, J. (2004).** Antibiotic use in animals—prejudices, perceptions and realities. *Journal of Antimicrobial Chemotherapy*, 53(1), 26-27.UK.USA.
- **Uyar, A., and Kl, M. (2012).** Value relevance of voluntary disclosure: evidence from Turkish firms.*Journal of Intellectual Capital*, 13(3), 363-376.
- **Van der Spiegel, M. (2004).** Measuring effectiveness of food quality management.
- **Van Donkersgoed, J; Graham, T., and Gannon, V. (1999).** The prevalence of verotoxins, Escherichia coli O157: H7, and Salmonella in the

feces and rumen of cattle at processing. *The Canadian Veterinary Journal*, 40(5), 332.

- **Van Koten-Vermeulen, J. E. M; Wouters, M. F. A., and Van Leeuwen, F. X. R. (1993).** Report of the 40th meeting of the joint FAO/WHO expert committee on food additives (JECFA). *World Health Organisation*, Geneva, 85.
- **Van Peteguem, C., and Daeselaire, E. (2004**):Residues of growth promoters. In L. M. L. Nollet (Ed.), *Handbook of food analysis* (2nd ed.) (pp. 1037–1063).
- **Van Poucke, L. S. G; Depourcq, G. C. I., and Van Peteghem, C. H. (1991).** A quantitative method for the detection of sulfonamide residues in meat and milk samples with a high-performance thin-layer chromatographic method. *Journal of chromatographic science*, 29(10), 423-427.
- **Van Rhijn, J. A; Lasaroms, J. J. P; Berendsen, B. J. A., and Brinkman, U. T. (2002).** Liquid chromatographic–tandem mass spectrometric determination of selected sulphonamides in milk. *Journal of chromatography A*, 960(1-2), 121-133.
- **Varelis, P; Beck, J; KEFEI, W. and Ghosh, D., (2008).** Analysis of melamine and cyanuric acid in food matrices by LC-MS-MS. LC GC *North America*, (JUN), pp.41-41.
- **Veggeland, F., and Borgen, S. O. (2002).** Changing the Codex: The role of international institutions. *Notat (Norsk institutt for landbruksøkonomisk forskning*: trykt utg.
- **Verbeke, W; Frewer, L. J; Scholderer, J., and De Brabander, H. F. (2007).** Why consumers behave as they do with respect to food safety and risk information. *Analytica chimica acta*, 586(1-2), 2-7.

- **Veritas, B. (2007).** *Hydrostar for experts user manual*. Research Department of Bureau Veritas.
- **Veritas, D. N. (2009).** co2qualstore: Guideline for selection and qualification of sites and projects for geological storage of co2. *dnv Report*, (2009-1425).
- **Von Hoff, D. D; Ramanathan, R. K; Borad, M. J; Laheru, D. A; Smith, L. S; Wood, T. E., and Zhang, H. (2011**). Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *Journal of Clinical Oncology*, 29(34), 4548.
- **Vroomen, L. H; Berghmans, M. C; Van Bladeren, P. J; Groten, J. P; Wissink, C. J., and Kuiper, H. A. (1990).** In vivo and in vitro metabolic studies of furazolidone: a risk evaluation. *Drug metabolism reviews*, 22(6-8), 663-676.
- **Wageh SD, Elsaid AE, Mohamed TE, Yoshinori ISN, Mayumi I (2013).** Antibiotic residues in food: *the African scenario Japanese Journal of Veterinary Research*, 61: 13-22.
- **Wahaballa, A. M; Kurauchi, F; Takagi, A., and Othman, A. M. (2011).** Modeling Departure Time Adjustment Behavior Considering Travel Time Variability Using Adaptive Neuro-Fuzzy Inference System. *In Proceedings of Infrastructure Planning* (Vol. 43).
- **Walker, B. F. (2000).** The Prevalence of Low Back Pain: a Systematic Review of the Literature from 1966 to 1998. *Clinical Spine Surgery*, 13(3), 205-217.
- **Walsh, V. (2003).** A theory of Magnitude: Common Cortical Metrics of Time, Space and Quantity. *Trends in Cognitive Sciences*, 7(11), 483-488.

- **Waltner-Toews, D. and S.A. McEwen. (1994a).** Residues of hormonal substances in foods of animal origin: a risk assessment. *Preventive Veterinary Medicine*, *20*(3), pp.235-247.
- **Waltner-Toews, D. and S.A. McEwen. (1994b).** Residues of Antibacterial and Antiparasitic Drugs in Foods of Animal Origin: a Risk Assessment. *Prev. Vet. Med*. 20:219-234.
- **Wang, J; Wang, W; Kollman, P. A., and Case, D. A. (2006).** Automatic Atom Type and Bond Type Perception in Molecular Mechanical Calculations. *Journal of Molecular Graphics and Modelling*, 25(2), 247-260.
- **Wang, S; Zhang, H. Y; Wang, L; Duan, Z. J., and Kennedy, I. (2006).** Analysis of sulphonamide residues in edible animal products: A review. *Food additives and contaminants*, 23(4), 362-384.
- **De Wasch, K., Okerman, L., De Brabander, H., Van Hoof, J., Croubels, S. and De Backer, P. (1998).** Detection of residues of tetracycline antibiotics in pork and chicken meat: correlation between results of screening and confirmatory tests. *Analyst*, 123(12), pp.2737-2741.
- **Weaver, L. (1992).** Antibiotic Residues in Milk and Meat: Perceptions and Realities. *Vet Med* 12: 1222-1228
- **Weber, T; Auer, J; O'rourke, M. F; Kvas, E; Lassnig, E; Berent, R., and Eber, B. (2004).** Arterial Stiffness, Wave Reflections, and the Risk of Coronary Artery Disease. *Circulation*, 109(2), 184-189.
- **White, E. R., and Zarembo, J. E. (1981).** Reverse phase high speed liquid chromatography of antibiotics. *The Journal of Antibiotics*, 34(7), 836-844.
- **WHO (1993).** Training Considerations for the Application of the Hazard Analysis Critical Control Points System to Food Processing and

Manufacturing, WHO Document, WHO/FNU/FOS/93.3, World Health Organization, Division of Food and Nutrition, Geneva.

- **WHO Regional Office for Africa (2004).** Developing and Maintaining Food Safety Control Systems for Africa. Current Status and Prospects for Change, Second FAO/WHO *Global Forum of Food Safety Regulators*, Bangkok, Thailand, 12-14 October 2004
- **Willis, H. L. (Ed.). (2000**). Distributed Power Generation: Planning and Evaluation. *Crc Press*.
- **Wongtavatchai, J; López-Dóriga, M. V., and Francis, M. J. (2010**). Effect of AquaVacTM VibromaxTM on Size and Health of Post Larva Stage of Pacific White Shrimp Litopenaeus Vannamei and Black Tiger Shrimp Penaeus Monodon. *Aquaculture*, 308(3-4), 75-81.
- **World Health Organization. (2007),** "Food Safety and Food Illness Fact Sheet", Available at: http://www.who.int/mediacentre/factsheets/fs237/en/
- **World Health Organization. (2009).** Global tuberculosis control: epidemiology, strategy, financing: *WHO report* 2009. World Health Organization.
- **Wright G. D. (2010).** Q and A: Antibiotic Resistance: Where does it come from and what can we do about it? *BMC Biol.* 8:123. http://doi.org/10.1186/1741-7007-8-123.
- **Wu, J., and Lederer, A. (2009).** A meta-analysis of the Role of Environment-based Voluntariness in Information Technology Acceptance. *Mis Quarterly*, 419-432.
- **Xu F., Xu H., Wang X., Zhang L., Wen Q., Zhang Y. & Xu W. (2014).** Discovery of N-(3-(7H-purin-6-yl)thio)-4-hydroxynaphthalen-1-yl)-sulfonamide derivatives as novel protein kinase and angiogenesis inhibitors

for the treatment of cancer: synthesis and biological evaluation. Part III. *Bioorg. Med. Chem.* 22(4):1487-1495.

- **Yamada, Y; Sasaki, J; Matsuzaki, T. and Shiiki, K. (1981).** Influence of Medium and Diluent pH and Diffusion Time on Antibiotic Bioassay. *Tokai J.Exp. Clin. Med*. 6, 23-33.
- **York, V. K; Brannon, L. A; Shanklin, C. W; Roberts, K. R; Barrett, B. B., and Howells, A. D. (2009).** Intervention Improves Restaurant Employees' Food Safety Compliance Rates. *International Journal of Contemporary Hospitality Management, 21(4), 459-478*.
- **Yorke, J. C., and Froc, P. (2000).** Quantitation of Nine Quinolones in Chicken Tissues by High-Performance Liquid Chromatography with Fluorescence Detection. *J Chromatography A*. 882: 63-77.
- **Yunus, Abdul Aziz. (2017)**.Antibiotic Residuce in Offal (fat, liver and kidney) samples from kumasi abattoir.
- **Zakeri, B., and Wright, G. D. (2008)**. Chemical Biology of Tetracycline Antibiotics. *Biochemistry and Cell Biology*, 86(2), 124-136.
- **Zeleny, R; Kolarich, D; Strasser, R., and Altmann, F. (2006).** Sialic Acid Concentrations in Plants are in the Rrange of Inadvertent Contamination. *Planta*, 224(1), 222-227.
- **Zuo, P., and Ye, B. C. (2006):** Small Molecule Microarrays for Drug Residue Detection in Foodstuffs.*Journal of Agricultural and Food Chemistry*, 54, 6978–6983.
- **Zuo XN; Xu T; Jiang L; Yang Z; Cao XY., (2012).** Toward Reliable Characterization of Functional Homogeneity in the Human Brain: Preprocessing, Scan Duration, Imaging *Resolution and Computational Space*. Epub 65: 374-386.

- **Zuo, X. N; Xu, T; Jiang, L; Yang, Z; Cao, X. Y; He, Y., and Milham, M. P. (2013).** Toward Reliable Characterization of Functional Homogeneity in the Human Brain: Preprocessing, Scan Duration, *Imaging Resolution and Computational Space.* Neuroimage, 65, 374-386.
- **21CFR225, 2010.** Code of Federal Regulations: *Current good manufacturing practice* for Title 21, Part 225.
- **21CFR226, 2010**. Code of Federal Regulations: *Current good manufacturing practice* for Type A medicated article. Title 21, Part 226.
- **21CFR500.86, 2010**. Code of Federal Regulations: Marker residue and target tissue. Title 21 Part, 500 Section 86.
- **21CFR530 2010**. Code of Federal Regulations: Extra label drug use in animals. Title 21, Part 530.

Appendices

1. The Questionnaire

The Factor	Practitioner	Pharmacist	Slaughter house officer	Other
SPECILIZATION	12	10	2	1

The factor	35-25	45-36	54-46
Age	18	6	1

The Factor	Bachelor	Master	PhD
DEGREE	18	7	0

The Antibiotics and the Veterinarians Awareness

The Factor	OXYTETRACYCLINE	SULPHONAMIDE	QUINOLONES	CHLORAMPHENICOL	AMINOGLICOSIDE	I HAVE NO IDEA
WHAT IS THE MOST ANTIBIOTIC/S USED IN YOUR WORK	18	2	2	2	1	0
WHAT IS THE MOST ANTIBIOTIC/S USED FOR THE TREATMEN OF CALVES ,LAMBS AND POULTRY IN YOUR WORK	3	6	8	3	0	0
FROM YOUR KNOWLEDGE ,WHAT IS HARMFUL ANTIBIOTICS FOR ANIMALS HEALTH	0	6	2	12	4	1
FROM YOUR KNOWLEDGE ,WHAT IS HARMFUL ANTIBIOTICS RESIDUCE FOR HUMAN HEALTH	5	1	5	11	0	3

The Factor	YES	NO	I HAVE NO IDEA
ARE THERE AN ANTIBIOTICS THAT HAVE BEEN BANNED GLOBALLY	18	4	3

THE ANTIBIOTICS BELOW WERE PREVENTED FROM USE IN PRODUCING ANIMALS	YES	NO	I HAVE NO IDEA
OXYTETRACYCLINE	4	13	8
SULPHONAMIDE	4	13	8
QUINOLONES	10	7	8
CHLORAMPHENICOL	13	4	8
AMINOGLICOSIDE	1	8	16

The Factor	OXYTETRA CYCLINE	QUINO LONES	CHLORAMP HENICOL	AMINOGLI COSIDE	I HAVE NO IDEA
COULD YOU MINTEION THE NAME OF AN ANTIBIOTICS THAT HAS BEEN BANNED FOR USE IN ANIMALS EATEN BY HUMAN	2	7	9	2	5

The Factor	YES I AM	THE OWNERS/WORKERS
DO YOU TREAT THE SICK ANIMALS WITH YOUR SELF OR THE OWNERS / WORKERS FOLLOW THE ANTIBIOTICS CORSE?	**2**	**23**

The Factor	YES	NO	SOMETIMES
DO YOU GIVE THE OWNER ATIPS ABOUT THE WITHDRAWAL PERIODE	15	1	0
DO THE OWNERS COMPLY WITH GUIDELINES	6	5	14
DO YOU ADHERE TO THE DOSAGE MENTIONED IN THE PRESCRIPTION	6	15	4

The Factor	YES	NO	Some of them
ARE YOU FAMILIAR WITH THE ANTIBIOICS WITHDRAWAL PERIODS	14	2	9

The Factor	YES	NO	I HAVE NO IDEA
DO YOU THINK THAT ADHERENCE TO DOSES IS IMPORTANT	17	8	0

2. The Antibiotics Residuce

The Factor	YES	NO	SOMETIMES	I HAVE NO IDEA
DO YOU CHECK THE ANTIBIOTICS RESIDUES AFTER SLAUGHTERING?	3	22	0	0

The Factor	YES	NO	I HAVE NO IDEA
DO YOU THINK THERE A TEST TO CHECK ANTIBIOTIC RESIDUES BEFORE SLAUGHTERING	5	9	11

The Factor	YES	NO	SOMETIMES
DO YOU CHECK THE ANTIBIOTICS RESIDUES BEFORE SLAUGHTER?	0	24	1

The Factor	ELIZA	I HAVE NO IDEA
WHAT TEST DO YOU THINK IS SUITABLE FOR ANTIBIOTICS RESIDUES SCREENING?	4	21

The Factor	1000- 50	2000- 1000	3000- 2000
APPROXIMATLY WHAT IS YOUR DAILY CONSUMPTION OF ANTIBIOTICS/ML	21	2	2

The Protection

HOW DO YOU PROTECT YOUR SELF DURING YOUR CONTACT WITH THE VETERINARY MEDICINES (ANTIBIOTICS)	YES	NO	SOMETIMES
WEARING GLOVES	7	10	8
WEARING LABCOAT	10	10	5
WEARING MASK	3	16	6
WEARING GLASS	1	19	5
HEAD COVER	0	2	23
WEARING OR CHANGING THE SHOESE	6	18	1

HOW DO YOU PROTECT YOUR SELF DURING THE TREATMENT OF SICK ANIMALS	YES	NO	SOMETIMES
WEARING GLOVES	12	5	8
WEARING LABCOAT	13	5	9
WEARING MASK	6	14	5
WEARING GLASS	0	24	1
HEAD COVER	0	21	4
WEARING OR CHANGING THE SHOESE	7	16	2

	Bovine	Caprine	Ovine	Processed Meat
Negative	53.6	87.5	3.6	72.7
Positive	46.4	12.5	96.4	27.3

Table (1) Frequency of positive and negatives

Bovine

	>2 mm	1-2 mm	Absent
Kidney	**1**	**6**	**21**
Liver	**2**	**4**	**22**
Lung	**1**	**4**	**23**
Heart	**0**	**5**	**23**
Muscle	**0**	**2**	**26**

Table (2) Inhibitory zone among species

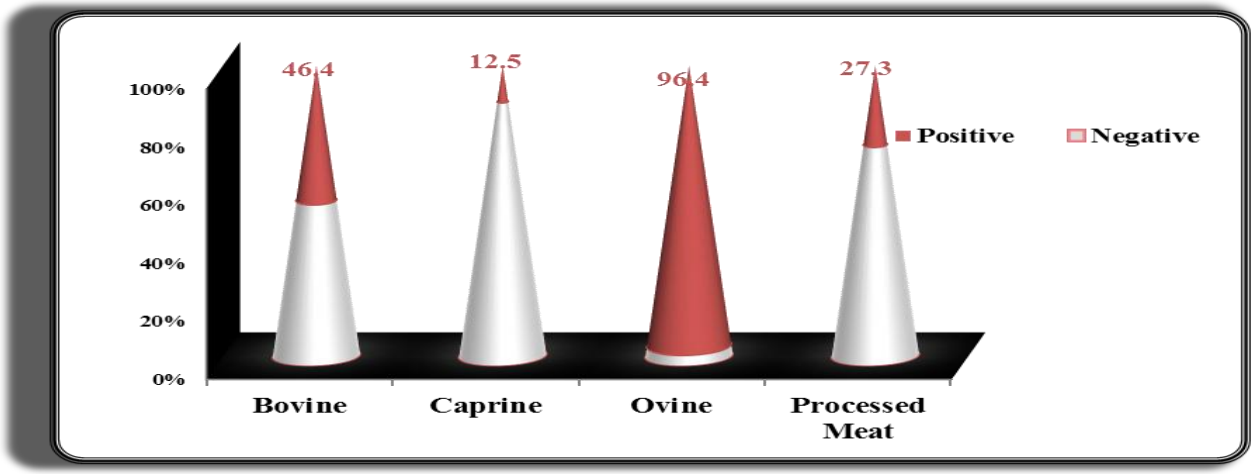

Figure (1): Absent and present in inhibition zones

Ovine

	Liver	Kidney	Muscle
>2 mm	15	6	12
1-2 mm	6	15	8
Absent	7	7	8

Table (3) Inhibitory zone among species

Caprine

	Liver	Kidney	Muscle
>2 mm	0	1	0
1-2 mm	1	0	0
Absent	7	7	8

Table (4) Inhibitory zone among species

Value	Frequency	Percent
Positive	3	27.3%
Negative	8	72.7%
Total	11	100.0%

Table (5) Processed Meat

Questionnaire analysis

Table (6) illustrates the frequency and percentage for the age

Age	Frequencies	Percentage
25-30 years	18	72.0%
36-45 years	6	24.0%
46-56 years	1	4.0%
Total	25	100.0%

Source: IPM SPSS 24 package

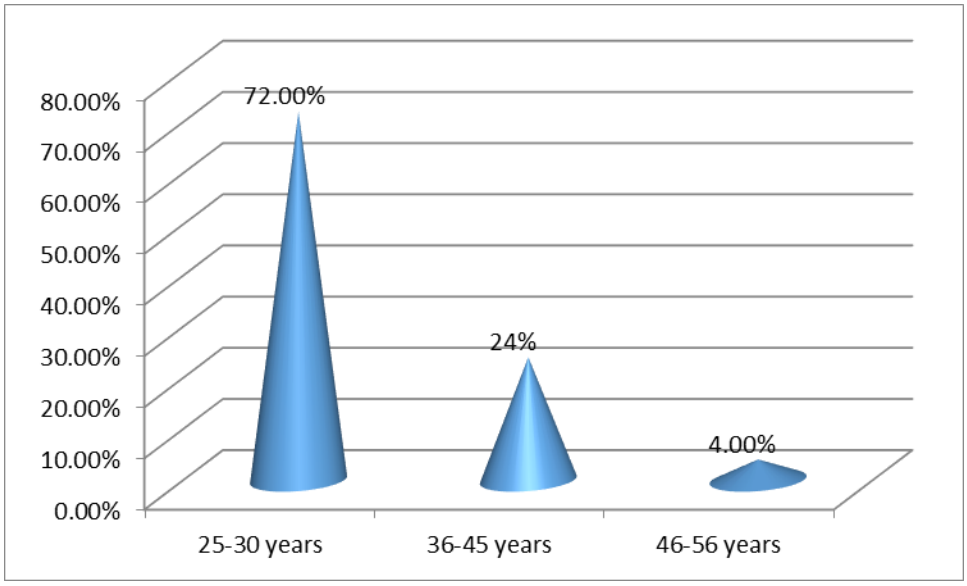

Diagram (1)

Table (7) illustrates the frequency and percentage for SPECILIZATION

Value	Frequencies	Percentage
Practitioner	12	48.0%
Pharmacist	10	40.0%
Slaughter house officer	2	8.0%
Other	1	4.0%
Total	25	100.0%

Source: IPM SPSS 24 package

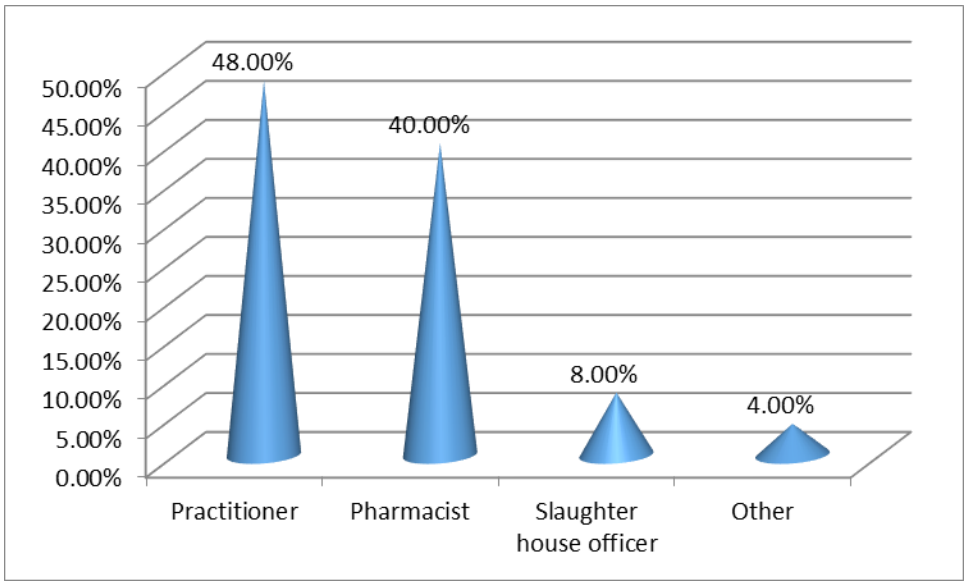

Diagram (2)

Table (8) illustrates the frequency and percentage for DEGREE

Value	Frequencies	Percentage
Bachelor	18	72.0%
Master	7	28.0%
PhD	0	0.0%
Total	25	100.0%

Source: IPM SPSS 24 package

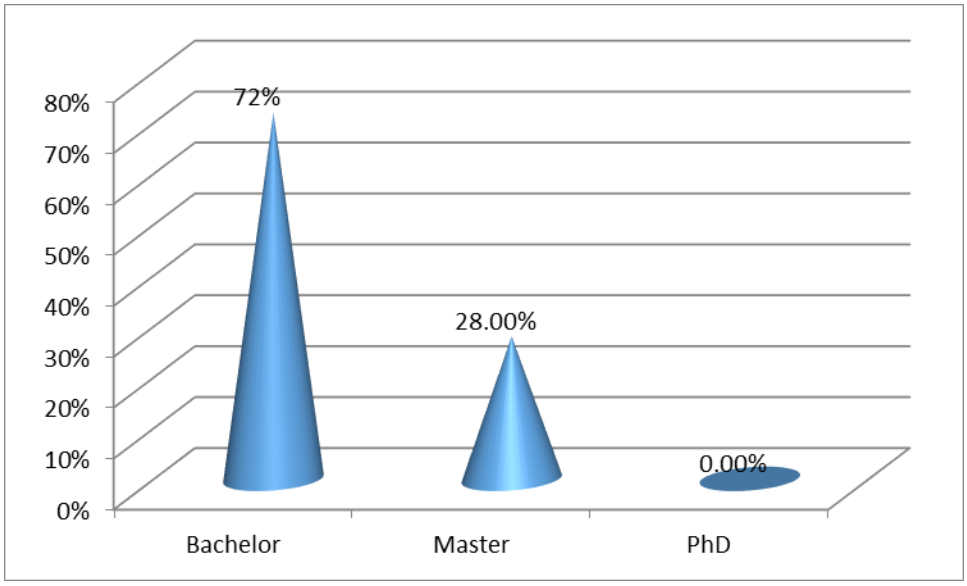

Diagram (3)

Table (9) illustrates the frequency and percentage for the ARE YOU FAMILIAR WITH THE ANTIBIOICS WITHDRAWAL PERIODS

Value	Frequencies	Percentage
Yes	14	56.0%
No	2	8.0%
SOMETIMES	9	36.0%
Total	25	100.0

Source: IPM SPSS 24 package

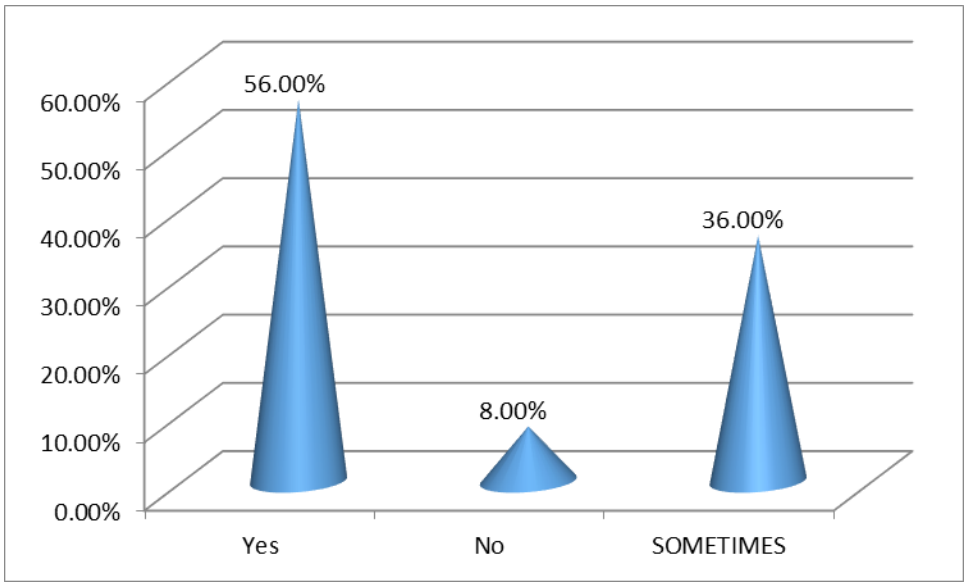

Diagram (4)

Table (9.1) illustrates chi-square teat results for the ARE YOU FAMILIAR WITH THE ANTIBIOICS WITHDRAWAL PERIODS

No	**Phrases**	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
1	ARE YOU FAMILIAR WITH THE ANTIBIOICS WITHDRAWAL PERIODS	8.72	2	0.02	3.0	Yes

Source: IPM SPSS 24 package

Table (10) illustrates the frequency and percentage for the DO YOU THINK THAT ADHERENCE TO DOSES IS IMPORTANT

Value	Frequencies	Percentage
Yes	17	68.0%
No	8	32.0%
SOMETIMES	0	0.0%
Total	25	100.0%

Source: IPM SPSS 24 package

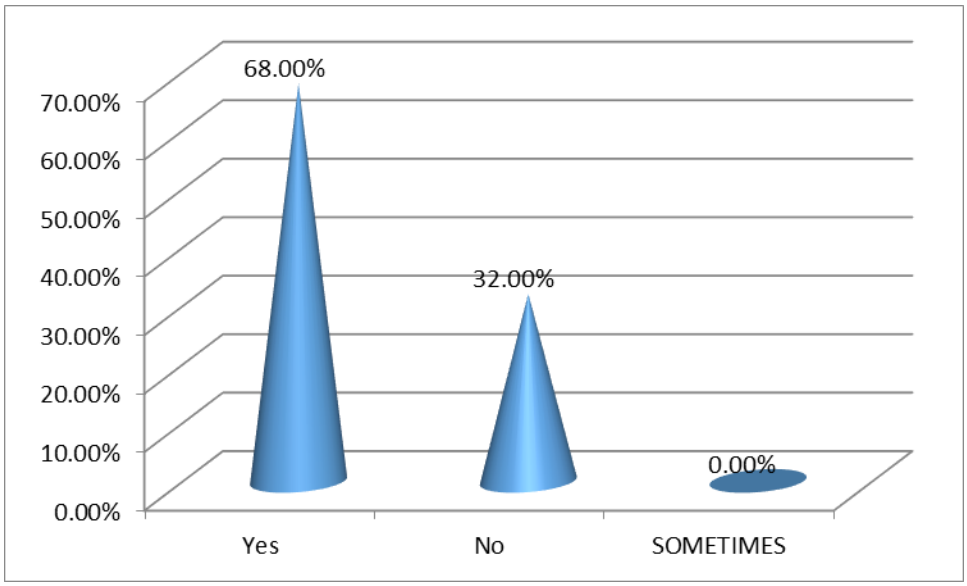

Diagram (5)

Table (10.1) illustrates chi-square teat results for the DO YOU THINK THAT ADHERENCE TO DOSES IS IMPORTANT

No	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
25	13.24	1	0.00	3.0	yes

Source: IPM SPSS 24 package

Table (11) illustrates the frequency and percentage for the HOW DO YOU PROTECT YOUR SELF DURING YOUR CONTACT WITH THE VETERINARY MEDICINES (ANTIBIOTICS)

No	**Items**	**Yes**	**NO**	**SOMETIMES**
1	WEARING GLOVES	7	10	8
		28.0	40.0	32.0
2	WEARING LABCOAT	10	10	5
		40.0	40.0	20.0
3	WEARING MASK	3	16	6
		12.0	64.0	24.0
4	WEARING GLASS	1	19	5
		4.0	76.0	20.0
5	HEAD COVER	0	2	23
		0.0	8.0	92.0
6	WEARING OR CHANGING THE SHOESE	6	18	1
		24.0	72.0	4.0

Source: IPM SPSS 24 package

Table (11.1) illustrates chi-square teat results for the HOW DO YOU PROTECT YOUR SELF DURING YOUR CONTACT WITH THE VETERINARY MEDICINES (ANTIBIOTICS)

No	**Phrases**	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
1	WEARING GLOVES	15.21	2	0.00	2	No
2	WEARING LABCOAT	19.20	2	0.00	2	No
3	WEARING MASK	14.25	2	0.00	2	No
4	WEARING GLASS	10.50	2	0.00	2	No
5	HEAD COVER	18.01	2	0.00	1	Sometime
6	WEARING OR CHANGING THE SHOESE	20.21	2	0.00	2	No

Source: IPM SPSS 24 package

Table (12) illustrates the frequency and percentage for the HOW DO YOU PROTECT YOUR SELF DURING THE TREATMENT OF SICK ANIMALS

No	**Items**	**Yes**	**NO**	**SOMETIMES**
1	WEARING GLOVES	12	5	8
		48.0	20.0	32.0
2	WEARING LABCOAT	13	5	9
		52.0	20.0	36.0
3	WEARING MASK	6	14	5
		24.0	56.0	20.0
4	WEARING GLASS	0	24	1
		0.0	96.0	4.0
5	HEAD COVER	0	21	4
		0.0	84.0	16.0
6	WEARING OR CHANGING THE SHOESE	7	16	2
		28.0	64.0	8.0

Source: IPM SPSS 24 package

Table (12.1) illustrates chi-square teat results for the HOW DO YOU PROTECT YOUR SELF DURING THE TREATMENT OF SICK ANIMALS

No	**Phrases**	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
1	WEARING GLOVES	12.96	2	0.00	3	Yes
2	WEARING LABCOAT	22.10	2	0.00	3	Yes
3	WEARING MASK	19.50	2	0.00	2	No
4	WEARING GLASS	15.24	1	0.00	2	No
5	HEAD COVER	10.10	1	0.00	2	No
6	WEARING OR CHANGING THE SHOESE	12.35	2	0.00	2	No

Source: IPM SPSS 24 package

Table (13) illustrates the frequency and percentage for the CHECK THE ANTIBIOTICS RESIDUES AFTER SLAUGHTERING

Value	Frequencies	Percentage
Yes	3	12.0%
No	22	88.0%
SOMETIMES	0	0.0%
I HAVE NO IDEA	0	0.0%
Total	25	100.0%

Source: IPM SPSS 24 package

Table (13.1) illustrates chi-square teat results for the DO YOU CHECK THE ANTIBIOTICS RESIDUES AFTER SLAUGHTERING

No	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
25	25.12	1	0.00	2.0	No

Source: IPM SPSS 24 package

Table (14) illustrates the frequency and percentage for the DO YOU THINK THERE A TEST TO CHECK ANTIBIOTIC RESIDUES BEFORE SLAUGHTERING

Value	Frequencies	Percentage
Yes	5	20.0%
No	9	36.0%
SOMETIMES	11	44.0%
Total	25	100.0

Source: IPM SPSS 24 package

Table (14.1) illustrates chi-square teat results for the DO YOU THING THERE A TEST TO CHECK ANTIBIOTIC RESIDUES BEFORE SLAUGHTERING

No	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
25	12.26	2	0.00	1.0	Sometime

Source: IPM SPSS 24 package

Table (15) illustrates the frequency and percentage for the DO YOU CHECK THE ANTIBIOTICS RESIDUES BEFORE SLAUGHTER

Value	Frequencies	Percentage
Yes	0	0.0%
No	24	96.0%
SOMETIMES	1	4.0%
Total	25	100.0%

Source: IPM SPSS 24 package

Table (15.1) illustrates chi-square teat results for the DO YOU CHECK THE ANTIBIOTICS RESIDUES BEFORE SLAUGHTER

No	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
20	25.89	1	0.00	2.0	No

Source: IPM SPSS 24 package

Table (15.2) illustrates chi-square teat results for the WHAT TEST DO YOU THINK IS SUITABLE FOR ANTIBIOTICS RESIDUES SCREENING

No	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
20	19.10	1	0.00	2.0	I have no idea

Source: IPM SPSS 24 package

Table (16) illustrates the frequency and percentage for the WHAT TEST DO YOU THINK IS SUITABLE FOR ANTIBIOTICS RESIDUES SCREENING

Value	Frequencies	Percentage
ELIZA	4	16.0%
I HAVE NO IDEA	21	84.0%
Total	25	100.0

Source: IPM SPSS 24 package

Table (17) illustrates the frequency and percentage for the APPROXIMATLY WHAT IS YOUR DAILY CONSUMPTION OF ANTIBIOTICS/ML

Value	Frequencies	Percentage
50-1000	21	84.0%
2000- 1000	2	8.0%
3000- 2000	2	8.0%
Total	25	100.0%

Source: IPM SPSS 24 package

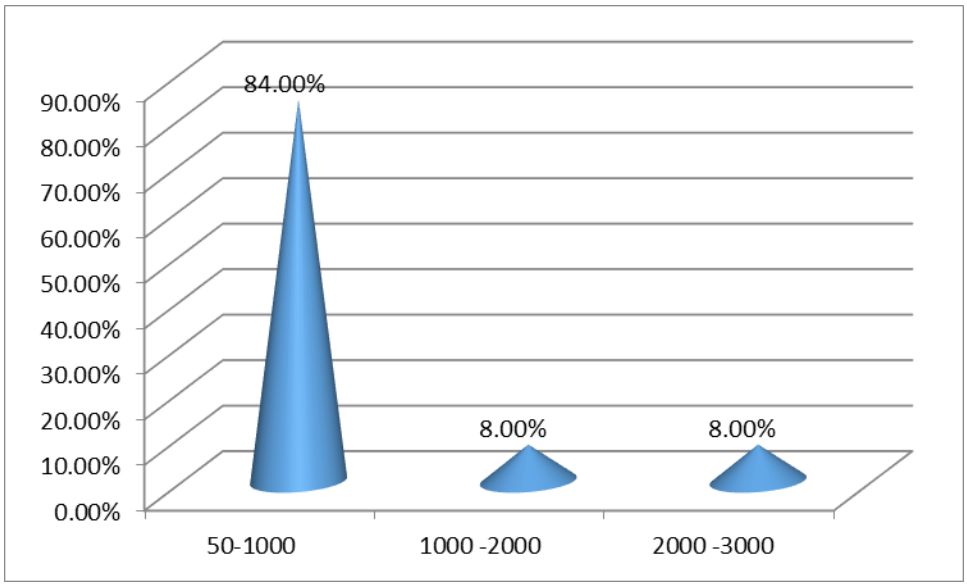

Diagram (6)

Table (18) illustrates chi-square teat results for the APPROXIMATLY WHAT IS YOUR DAILY CONSUMPTION OF ANTIBIOTICS/ML

No	Chi-square value	df	Sig.	Median	Interpretation
25	25.10	2	0.00	1.0	**50-1000**

Source: IPM SPSS 24 package

Table (19) illustrates the frequency and percentage for the ARE THERE AN ANTIBIOTICS THAT HAVE BEEN BANNED GLOBALLY

Value	Frequencies	Percentage
Yes	18	72.0%
No	4	16.0%
I HAVE NO IDEA	3	12.0%
Total	25	100.0%

Source: IPM SPSS 24 package

Table (20) illustrates the frequency and percentage for the

ANTIBIOTICS BELOW WERE PREVENTED FROM USE IN PRODUCING ANIMALS

No	**Items**	Yes	on	I have no idea
1	OXYTETRACYCLINE	4	13	8
		18.0	52.0	32.0
2	SULPHONAMIDE	4	13	8
		18.0	52.0	32.0
3	QUINOLONES	10	7	8
		40.0	28.0	32.0
4	CHLORAMPHENICOL	13	4	8
		52.0	18.0	32.0
5	AMINOGLICOSIDE	1	8	16
		4.0	32.0	64.0

Source: IPM SPSS 24 package

Table (21) illustrates chi-square teat results for THE ANTIBIOTICS BELOW WERE PREVENTED FROM USE IN PRODUCING ANIMALS

No	**Phrases**	**Chi-square value**	**df**	**Sig.**	**Median**	**Interpretation**
1	OXYTETRACYCLINE	12.25	2	0.00	2	No
2	SULPHONAMIDE	23.21	2	0.00	2	No
3	QUINOLONES	19.81	2	0.00	3	Yes
4	CHLORAMPHENICOL	10.14	2	0.00	3	Yes
5	AMINOGLICOSIDE	18.01	2	0.00	1	I have no idea

Source: IPM SPSS 24 package

Table (22) illustrates the frequency and percentage for the COULD YOU MINTEION THE NAME OF AN ANTIBIOTICS THAT HAS BEEN BANNED FOR USE IN ANIMALS EATEN BY HUMAN

Value	Frequencies	Percentage
OXYTETRACYCLINE	2	8.0%
QUINOLONES	7	28.0%
CHLORAMPHENICOL	9	36.0%
AMINOGLICOSIDE	2	8.0%

I HAVE NO IDEA	5	20.0%
Total	25	100.0%

Source: IPM SPSS 24 package

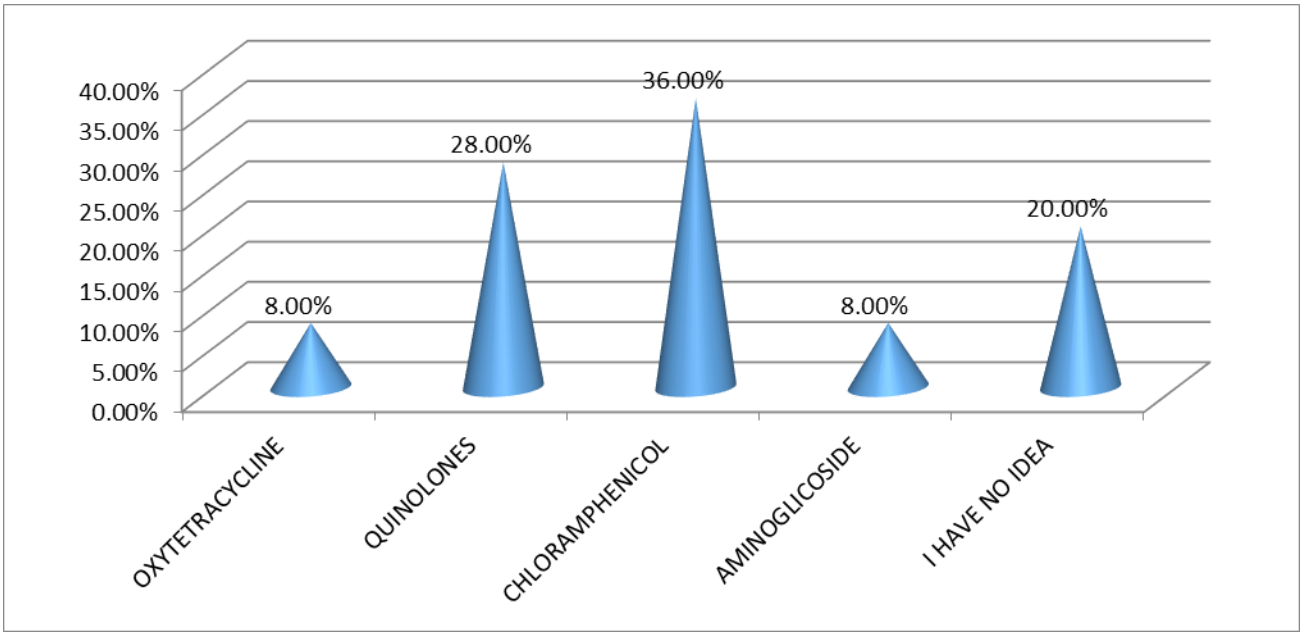

Diagram (7)

Table (23) illustrates chi-square teat results for the COULD YOU MINTEION THE NAME OF AN ANTIBIOTICS THAT HAS BEEN BANNED FOR USE IN ANIMALS EATEN BY HUMAN

No	Chi-square value	df	Sig.	Median	Interpretation
25	18.21	2	0.00	3.0	CHLORAMPHENIOL

Source: IPM SPSS 24 package

Table (24) illustrates the frequency and percentage for the DO YOU TREAT THE SICK ANIMALS WITH YOUR SELF OR THE OWNERS / WORKERS FOLLOW THE ANTIBIOTICS COUSE

Value	Frequencies	Percentage
YES I AM	2	8.0%
THE OWNERS/WORKERS	23	92.0%
Total	25	100.0%

Source: IPM SPSS 24 package

No	Phrases	Chi-square value	df	Sig.	Median	Interpretation
1	Do you give the owner a tips about the withdrawal period	17.64	1	0.00	3	Yes
2	Do the owners comply with guidelines	15.84	2	0.00	1	Sometime
3	Do you adhere to the dosage mentioned in the prescription	14.15	2	0.00	2	No

Table (4) illustrates chi-square teat results for the withdrawal periods