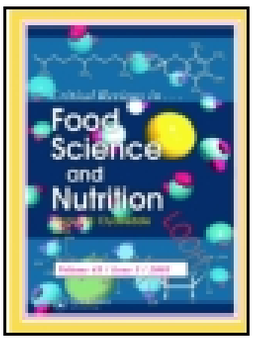

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Viral contamination in food products

Prevalence and Evaluation Strategies for Viral Contamination in Food Products: Risk to Human Health -- A Review

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**ABSTRACT**

Nowadays, viruses of foodborne origin such as norovirus and hepatitis A are considered major causes of foodborne gastrointestinal illness with widespread distribution worldwide. A number of foodborne outbreaks associated with food products of animal and non-animal origins, which often involve multiple cases of variety of food streams, have been reported. Although several

viruses, including rotavirus, adenovirus, astrovirus, parvovirus, and other enteroviruses, significantly contribute to incidence of gastrointestinal diseases, systematic information on the role of food in transmitting such viruses is limited. Most of the outbreak cases caused by infected food handlers were the source of 53% of total outbreaks. Therefore, prevention and hygiene measures to reduce the frequency of foodborne virus outbreaks should focus on food workers and production site of food products. Pivotal strategies, such as proper investigation, surveillance, and reports on foodborne viral illnesses, are needed in order to develop more accurate measures to detect the presence and pathogenesis of viral infection with detailed descriptions. Moreover, molecular epidemiology and surveillance of food samples may help analysis of public health hazards associated with exposure to foodborne viruses. In this present review, we discuss different aspects of foodborne viral contamination and its impact on human health. This review also aims to improve understanding of foodborne viral infections as major causes of human illness as well as provide descriptions of their control and prevention strategies and rapid detection by advanced molecular techniques. Further, a brief description of methods available for the detection of viruses in food and related matrices is provided.

Keywords

Food, Virus, Epidemiology, Detection, Prevalence

## INTRODUCTION

Viruses cause a wide variety of diseases in plants, animals, and humans. A group of individual viruses cause a specific disease, and each group of viruses has its own typical host range and cell preference known as tropism (Eterpi et al., 2010). To control severe viral infections, biotechnological approaches and associated food manufacturing processes need to be optimized (Eterpi et al., 2010). Moreover, food production also represents an increased risk of food products contaminated by viral infection (Koopmans and Duizer, 2004). Hence, understanding of viral pathology is continually evolving, including regular descriptions of new pathogenic strains and species (Arzt et al., 2010). Although most cases of foodborne illness caused by enteric viruses such as noroviruses (NOVs), rotaviruses, adenoviruses and astroviruses are not life-threatening and are short-lived, there is a lack of knowledge about sources of enteric viruses along with insufficient routine detection techniques and outbreak reports (Kurdziel et al., 2001). Fresh produce, including soft vegetables and fruits, might play a significant role in spreading viral infection. Major viral infections in humans, especially those associated with enteric viruses, are caused by human-to-human contacts (Koopmans, 2008).

The most frequently reported viruses associated with foodborne illness are NOV and hepatitis A virus (HAV). However, a range of other viruses, including hepatitis E virus (HEV), astrovirus, human rotavirus (HRV), sapovirus, enterovirus, coronavirus, adenovirus, parvovirus, and aichi virus, have been reported to be transmitted through foods and can survive for longer periods of time (FAO/WHO, 2008). As reported previously, viruses are classified into different groups based on their disease symptoms; gastroenteritis viruses cause gastrointestinal illness, hepatitis viruses cause enteric hepatitis, and enteroviruses proliferate in the intestine and cause



 

viral infection upon migration to other body organs (FAO/WHO, 2008). Generally, these viruses are scattered in human feces and may drive human illness upon discharge in the environment (FAO/WHO, 2008). There is huge interest in NOV and HAV of foodborne origins as significant causes of foodborne gastrointestinal viral infection.

Multiple viral infection cases involving foodborne outbreaks due to consumption of foods of animal and non-animal origins have been reported previously (Stals et al., 2013). Since the survival rate of pathogenic microbes including viruses, bacteria, and fungal spores on fresh produce such as raw fruits and vegetables is usually high, adequate minimal food processing steps including washing steps should be acquired (Butot et al., 2008). In addition, frozen and unprocessed fruits have also been considered major vectors of viral infection, especially in the case of HAV linked to toxin production, suggesting that adequate measures are needed to avoid the production of toxic products in food products (Butot et al., 2008). Viral contamination in the environment can occur easily through pre-harvesting, infected food handling, and cross-contamination in food establishments, therefore protection of produce from viral contamination has become a major concern of the food and agriculture industries. As reported previously, viral infections cause more than 5 million foodborne illnesses each year in the USA (Koopmans and Duizer, 2004). Among them, foodborne human NOV and HAV were found to be the most common viral etiologies of foodborne illnesses (Koopmans and Duizer, 2004).

European laws on hygiene food packaging highly recommended manufacturers to take all safety precautions for food quality to provide consumers contamination-free food products (ISO, 2013). Although strict rules and regulations have been imposed by European legislation on industries and related authorities to ensure a safe and viral contamination-free food supply to

consumers, it is very difficult to detect the presence of small viral particles in food produce (ISO, 2013). A prior CDC report confirmed Norwalk-like virus contamination and gastroenteritis illness at local health departments in North Wisconsin which was caused by person-to-person contact transmission (Hall et al., 2012). Cleaning of environmental surfaces and the availability and use of hand-washing facilities played major roles in resolving this viral illness (CDC, 2001). The latest epidemiological data by the CDC confirm that enteric viruses represent 13.1% and 45% of foodborne outbreaks in Europe (EFSA and ECDC, 2013) and the United States (Gould et al., 2014), respectively. Among the reported outbreaks of enteric viruses, human NOVs belonging to genogroups I and II display the greatest epidemiological effects (EFSA and ECDC, 2013; Gould et al., 2014; Hall et al., 2012).

Fresh produce vegetables have displayed the presence of HAV and Norwalk-like viruses, leading to major outbreaks of foodborne illness (Koopmans, 2008). During these outbreaks, exposure of oxygen-less packaging, as well as sewage and workers infected with viruses led to severe complications of foodborne illness (Holtby et al., 2001; Long et al., 2002). However, persistence of enteric viruses and factors responsible for viral contamination in fresh produce still need to be explored. A description of major outbreaks caused by enteric viruses is summarized in Table 1. According to the CDC, about 19 to 21 million norovirus cases, with 570 to 800 related deaths, are reported in the USA each year (CDC, 2015). During February 2016, outbreaks of NOV have been reported at Kansas City Dinner Theater, a Buffalo Wild Wings Inc. restaurant in Kansas, and several Chipotle Mexican Grill Inc. restaurants in the USA in which infections that have sickened more than 600 individuals and 100 students living in university of Michigan's main campus (FSN, 2016). Recent findings on foodborne illness caused by NOV in

the United States have confirmed an average of 365 foodborne outbreaks annually, resulting in an estimated 10,324 illnesses, 1,247 healthcare provider visits, 156 hospitalizations, and one death (Hall et al., 2012). Among these outbreaks, vegetable, fruit/nut, and mollusk commodities contributed about 33%, 16%, and 13% to viral outbreaks (Hall et al., 2012), respectively as schematically shown in Figure 1

Yu et al. (2010) reported the presence of NOV in two infected food handlers, leading to an outbreak of gastroenteritis illness in several elementary school students in Incheon city, Korea. Reports confirmed that the main cause of this outbreak was improper food processing of dried radish salad by the infected handlers. In Japan, a 19% outbreak frequency of NOV was reported in which infected food handlers caused about 73% of the outbreak, whereas non-infected food handlers contributed only 7% (Ozawa et al., 2007). Consumption of uncooked lettuce, carrot, and tap and spring water resulted in a community-based HAV outbreak in Korea in 2008 (Yoon et al., 2009). Although increasing incidence of HAV outbreaks among Korean military personnel and healthcare workers has been observed (Lee et al., 2008; Park et al., 2007), there are insufficient epidemiological studies on potential sources of infection and modes of transmission in the community-wide HAV outbreaks in Korea (Yoon et al., 2009).



**EPIDEMIOLOGY OF VIRAL CONTAMINATION**

Emerging infectious diseases are rapidly increasing with wide ranging geographical distribution and are defined as newly appearing infections in a human population (Morse, 2004). Generally, parasitic agents such as human enteric viruses replicate in the human intestine of infected hosts and are excreted in the feces. Since viruses are environmentally inert, they differ from foodborne pathogens in that they cannot replicate in food, water, or environmental samples.

In addition, unlike bacterial pathogens, human enteric viruses show environmental stability, are resistant to traditional methods used to control bacterial pathogens, and have notably low infectious doses (Hall et al., 2011). Nowadays, human enteric viruses are important causes of viral infection, leading to severe foodborne illness. However, low incidence of foodborne outbreaks caused by small round virus, parvovirus, and astrovirus has been reported (Cromeans et al., 2001). In developing countries, rotaviruses, adenoviruses, norovirus, and hepatitis E viruses are very frequently reported causes of waterborne disease outbreaks (Bosch et al., 2005).

Viral infections caused by HAV in children and adults affect the immune system, particularly in developing countries (Cuthbert, 2001). As reported previously, declining rate of immunity among populations has increased risk of severe foodborne outbreaks due to contaminated food imported from countries of high endemicity (ACMSF, 1998). Enteric viruses as causative agents of illness play a vital role in human diseases, and acute non-bacterial gastroenteritis is a well-known phenomenon after the discovery of Norwalk-like virus and rotavirus (Cheong et al., 2009). Severe complications such as diarrhea in infants and kids have been reported for rotavirus and, Norwalk-like viruses also significantly contributes to infant gastroenteritis (Elliott, 2007). Since its discovery in 1974, enterovirus 71 was reported to cause severe neurological disease linked to paralysis complications (Ho, 2000; Thong, 2000). Similar outbreaks of neurological disease caused by Coxsackie virus A7 and Entero 70 have also been reported (Julius et al., 2009). Moreover, polioviruses and enterovirus have been found to be the most important causative agents of life-threatening infections with neurological involvement or even fatal disease (Julius et al., 2009).

**ROUTE OF TRANSMISSION OF VIRAL INFECTION**

NOVs, considered to be major foodborne viruses, have been found to cause severe foodborne outbreaks in Europe and the USA in 2007-2008 and 2007, respectively (EFSA and ECDC, 2013). Besides NOVs, HAV is considered to be the most significant causative agent of complex foodborne outbreaks. A major proportion of severe foodborne outbreaks is due to contact with human feces, which contain up to $10^7$ viral particles per gram of human stool (Hall et al., 2011).

In general, foodborne viruses are highly adaptable, resulting in an increased rate of food contamination through the food chain cycle (EFSA and ECDC, 2013). However, these viruses also show various degrees of resistance to environmental stresses, including acid, heat, drying, pressure, disinfectants, and ultraviolet radiation (EFSA and ECDC, 2013). In addition, although viruses have different routes of transmission, major causes of viral infectious outbreaks are introduction of viral particles to immune-sensitive populations through the food supply, tap water supply, asymptomatic shedding, person-to-person direct contact, as well as by any contaminated environmental sources (EFSA and ECDC, 2013). Figure 2 describes the various modes of viral transmission/contamination.

***Human Sewage and Feces***

Reports have confirmed that commonly used methods for treatment of sewage and feces cannot sufficiently remove or inactivate viral transmission to humans (Van den Berg et al., 2005). Similar research conducted in Europe, Japan, and the USA observed that sewage samples showed the presence of viral particles of human enteric viruses even after treatment (Villar et al., 2007; Silva et al., 2007; Gregory et al., 2006; Myrmel et al., 2006). In general, person-to-person contact among sewage treatment workers is considered to be the main route of viral infection

(Cromeans et al., 2001). Food processing and pre-harvesting of fresh produce using viral contaminated sewage water also significantly contributes to food production, contaminated with multiple viral particles (Silva et al., 2007). Multiple viral contamination has resulted in simultaneous infection of people with multiple viral strains, including infection by animal rotaviruses (Symes et al., 2007; Iturriza-Gomara et al., 2001). All these mechanisms contribute to the diversity of virus strains individually or synergistically (Iturriza-Gomara et al., 2001).



***Infected Food Handlers***

Human populations infected by the virus may shed the virus even before developing symptoms and long after recovery. Recently, Amar et al. (2007) reported highe levels (more than 107 viral particles per gram of stool sample) of asymptomatic shedding. Food handlers may have hands contaminated with the human enteric virus if their stool is contaminated or come into contact with feces while cleaning toilet areas without proper hygiene. Such viruses can be transmitted from any part of the human body, including the skin, hands, and fingers, to food and are considered as secondary sources of viral contamination (Bidawid et al., 2000a; Bidawid et al., 2004). Consequences of human handling of food or fresh produce may lead to viral contamination at any stage of the farm to fork continuum, which mainly includes handling of produce with infected hands during harvesting, packaging, transport, and retail establishments (Bidawid et al., 2000b). Produce can also be contaminated with the virus during packaging. NOV is known to cause vomiting, and a number of NOV outbreaks have occurred due to exposure to vomit containing NOV (Bidawid et al., 2000b; Bidawid et al., 2004). Viruses are tough environmental survivors and display resistance to various environmental factors such as cleaning agents and disinfectants (Bidawid et al., 2004).

### *Zoonotic Transmission*

Zoonotic refers to viruses of animal origin that infect humans. Consumption of oysters as a passive carrier of human enteric virus can cause viral infection in humans. Oysters infected with viral particles subsequently transmit these particles to human beings. Any virus of animal origin transmitted via meat consumption by humans may cause viral outbreaks in a process called zoonotic infection. As reported previously, consumption of raw animal meat such as pig meat, deer liver, and wild boar may cause severe complications due to HEV viral infection (Tei et al., 2003; Takahashi et al., 2004). Moreover, ready to eat pig livers sold at supermarkets are known to cause severe cases of HEV viral infections in the Japan, USA, and the Netherlands (Yazaki et al., 2003; Feagins et al., 2007; Rutjes et al., 2007). Consumption of uncooked boar meat, including liver, kidney, and intestine, was shown to cause a significant increase in HEV viral infection in Germany (Van der Poel, 2014). The severity and mode of HEV transmission may depend on the virus genotype, environmental conditions, hygienic conditions, and types of consuming foods (Van der Poel, 2014).

## STABILITY OF FOODBORNE VIRUSES DURING FOOD PROCESSING

In general, enteric viruses show resistance to current food processing and preservation methods. Although the survival rates of foodborne viruses differ under different processing and substrate conditions, viruses of food origin can generally survive under a wide range of acidic and alkaline conditions (pH 3 to 10) (Sun et al., 2012). As reported previously, pasteurization of milk inactivates HAV, whereas prolonged heat treatment is needed to inactivate HAV virus in bivalve mollusks (Van der Poel, 2014). In addition, some enteric viruses have acquired resistance against ionizing radiation, leading to the application of higher controlling doses with negative

impacts on the organoleptic properties of food products (Sun et al., 2012). For example, screening of green onion for HAV at different temperatures (3 to 23°C) confirmed less survival of HAV at higher temperatures losing only 1 $\log_{10}$ inactivity after 5 days at 23°C (Sun et al., 2012). Reports have confirmed that the application of water alone or in combination with disinfectants while washing fresh produce may able to reduce about 1-2 $\log_{10}$ amount of virus (Sun et al., 2012). In addition, refrigeration and freezing of produce have minor effects on the survivability of viruses, but also are considered to be an important process of virus preservation in some food products (Papafragkou et al., 2006). Since severe concerns have been raised regarding persistence of viral particles in food processing strategies, effective control measures and prevention strategies are needed to control proliferation of foodborne viruses, especially at pre-harvest/post-harvest levels from the farm to ready-to-eat home products. Viral persistence in food produce contaminated at any stage is well reviewed in the epidemiological literature (Papafragkou et al., 2006).



## STRATEGIES FOR INACTIVATION OF VIRUS FROM FOOD PRODUCTS

For effective removal or inactivation of viral particles, a number of methods are used in the biopharmaceutical industry for inactivation of virus particles, including ultraviolet irradiation, heating, and solvent and detergent treatments (Tsujimoto et al., 2010). However, these methods are limited with regards to biological products from a cell line-based bioreactor and plasma-derived biologicals (Charlebois et al., 2001; Unger et al., 2009). As reported previously, the ability of detergents to inactivate pseudorabies rhFIX virus production from transgenic products has been confirmed, with reference in milk samples (Chang et al., 2010).

### *Thermal Treatments*

Proper inactivation of viral proteins can be achieved at ambient temperature, which disrupts the viral protein (Bidawid et al., 2000b). Significant reduction of viral particles up to 3 $\log_{10}$ has been obtained through heating at 56-60°C in laboratory media or buffer (Hirneisen et al., 2009). Thermal inactivation curves for several viruses show a biphasic nature. However, thermal stability has been observed for few viruses, which may either aggregate together or attach to protective food constituents (Bidawid et al., 2000b). Moreover, dried surfaces of viruses show extreme resistance to heat inactivation, especially in the presence of organic materials (O'Dea et al., 2008). A porcine circovirus can survive for 30 min at 120°C, whereas other skin disease viruses can hold their infectivities for about 10 min at 100°C, in addition, adenovirus can survive up to 10 min at 80°C upon drying (O'Dea et al., 2008). Further, cooking and commercial thermal processes have not produced positive results for virus activation in various food products (Bidawid et al., 2000b). Specifically, a number of viruses, including NOV, HAV, poliovirus, and other enteric viruses, remain active or in infective phase in shellfish even after steaming for about 47 sec at 70°C (Hirneisen et al., 2009). However, inactivation of HAV and NOV has been achieved by dipping shellfish in boiling water for 3 min (Hewitt and Greening, 2006).

***Irradiation***

Although irradiation could be an important strategy for inactivation of viral proteins or viruses, a high irradiation dose could have severe side effects on the quality or organoleptic properties of food products (Feng et al., 2011). Viruses display resistance to irradiation, although its resistance frequency depends on the size and low moisture contents of viruses. Feng et al. (2011) performed a systematic study on the inactivation of human norovirus surrogate (murine norovirus 1: MNV-1), human norovirus virus-like particles (VLPs), and vesicular stomatitis

virus (VSV) by gamma irradiation and demonstrated that MNV-1 and VLPs were resistant to gamma irradiation. For MNV-1, at the dose of 5.6 kGy, only 1.7 to 2.4 log virus reduction was observed in fresh produce. However, VSV was more susceptible to gamma irradiation with a viral log reduction rate of 3.3 at the same dose in Dulbecco's modified Eagle medium. The beam irradiation D values for inactivation of low pathogenicity avian influenza virus was found to be 1.6 kGy in egg white and 2.6 kGy in ground turkey (Brahmakshatriya et al., 2009). In addition, irradiation D values for inactivation of poliovirus, HAV, and rotavirus in oysters were found to be 2.94, 2.0, and 2.4 kGy, respectively (Baert et al., 2009).

***High Pressure***

High hydrostatic pressure methods have been effectively used to inactivate viruses under certain optimized conditions (Baert et al., 2009; Kingsley et al., 2007; Grove et al., 2006). Significant reduction up to 7-8 $\log_{10}$ units was achieved upon exposure of HAV and rotavirus to 450 MPa at 22ºC for 5 min (Grove et al., 2006). Although inactivation of virus particles has been achieved using high pressure techniques, rotaviruses have potent resistance to this technology when suspended in virus-reducing buffer containing high salt and sucrose (Khadre and Yousef, 2002). Large capsid proteins protect virus particles from hydrostatic pressure, particularly poliovirus and aichi virus show about <1 $\log_{10}$ reduction in virus titer upon exposure to hydrostatic pressure at 600 MPa, and 20ºC for 60 min (Ferreira et al., 2009). Virus-reducing media consisting of high salt and sucrose may protect viruses from high pressure effects as observed in the case of HAV and feline calicivirus (Kingsley and Chen, 2008; Grove et al., 2009). Moreover, freezing and refrigeration can be used for viral deactivation, and HAV has been found to be very sensitive to hydrostatic pressure techniques (Kingsley et al., 2007). A

report confirmed that titer of highly pathogenic avian influenza of subtype H7N7 virus suspended in chicken meat is reduced about 5 $\log_{10}$ upon treatment at 500 MPa for 25 sec at 15°C (Isbarn et al., 2007).

***Ultraviolet Light***

UV light primarily damages the RNA and DNA of viruses, although it can damage proteins at very high doses (Grove et al., 2009). Thymine or uracil dimers are produced in nucleic acids and result in mutations (Eischeid et al., 2001). Double-stranded DNA and RNA viruses are more resistant to UV light since only one strand is damaged while the other strand can serve as a template for repair (Hirneisen et al., 2010; Eischeid et al., 2001). Adenoviruses are more resistant to UV than other enteric viruses (Hirneisen et al., 2010). A lower or optimum range of ultraviolet light at 271 nm wavelength has been shown to be a more effective disinfectant than others (Kingsley et al., 2007).

***Sanitizers and Disinfectants***

Sanitizers and disinfectants can inactivate viruses as well as bacteria, but their effectiveness depends on temperature, viral concentration and aggregation, viral structure and size, and the presence of organic matter or dirt (Hirneisen et al., 2010). Viruses with lipid envelopes are generally more susceptible to disinfectants than non-enveloped viruses (Hirneisen et al., 2010). Many animal viruses are surrounded by a lipid layer, whereas human enteric viruses and some animal viruses, including bluetongue, HEV, parvovirus, circovirus, and swine vesicular disease virus, do not have a lipid envelope and can be more difficult to control (Hirneisen et al., 2010). Some viruses, including porcine parvovirus, are very resistant to disinfectants that are generally effective against non-enveloped viruses (Eterpi et al., 2009).

## RECENT ADVANCES IN DIAGNOSTIC APPROACHES FOR VIRAL CONTAMINATION

Despite the availability of various virus inactivation methods, detection of virus particles has become a hurdle to the food industry due to the low number of viral particles. A number of viral detection methods have been described for detection of human enteric virus in foods (Bidawid et al., 2000b; Dubois et al., 2002; Le Guyader et al., 2004; Rutjes et al., 2006). A description of the methodologies used in virus detection is summarized in Table 2.

Virus detection in food produce can be controlled by efficiently extracting the viral genome since detection of viral particles at the molecular level depends on the concentration of the viral genome extracted (Dubois et al., 2002). However, to date, there is no adequate method available for extraction of the viral genome. Hence, a model virus is added to the sample at a known concentration before its extraction in order to control efficiency of the extraction process (Pinto and Bosch, 2008).

### *Real-Time polymerase chain reaction (RT-PCR)-Based Detection Methods*

In the RT-PCR detection system, detection of virus is followed by two steps: propagation of infectious viruses in cell culture and/or amplification of viral genomes by PCR or RT-PCR. These techniques have several advantages in extracting nucleic acids from viruses since they are high-speed techniques, sensitive and reproducible and minimize contamination. A number of detection methodologies were developed for virus detection (Casas et al., 2007; Houde et al., 2007) based on RT-PCR methods for HAV detection in food (Sanchez et al., 2007). These RT-PCR molecular techniques not only assist the quantitative and qualitative analysis of



 

viral genomes but also provide a method for quantitative hazard risk assessment analysis, which is critical for several public health actions (Sanchez et al., 2007).

In addition, a one-step immunocapture RT-PCR detection method was developed for the detection of barley stripe mosaic virus in barley seedlings (Zarzynska et al., 2014). However, the detection sensitivity of this method was about 50 fg/µL of total viral RNA detection under optimal reaction conditions (Zarzynska et al., 2014). Latil et al. (2012) developed a method based on viral concentration using RNA extraction and RT-qPCR amplification steps. One-step duplex RT-qPCR was developed for detection of HEV and murine norovirus with detection limits of 700 to 3500 HEV genome copies/0.5 L bottled water and 3500 HEV genome copies/0.5 L tap water, respectively.

An anion exchange resin-based method developed for detection of enteric virus and measurement of F-RNA coli phage concentration in water samples showed a detection limit of $10^0$ PFU/mL to $10^{-1}$ PFU/mL (Pérez-Méndez et al., 2014). Hamza et al. (2014) developed a multiplex Luminex assay for effective detection of waste water viruses, including human adenovirus, polyomavirus, enterovirus, rotavirus, and norovirus genogroups I and II, with an analytical sensitivity comparable to that of qPCR, making it a reliable method for simultaneous detection of waste water viral pathogens. However, of the major limitations of PCR is its inability to differentiate between infectious and non-infectious viruses (Pérez-Méndez et al., 2014).

***Biosensor-Based Detection Methods***

Recently, application of biosensor technology to detection of pathogenic microbes, including viruses, has gained attention. The sensitivity of biosensor techniques depends on

transducer properties and the recognition element with applications to nano-devices, micro-devices, and sample treatment (Florescu et al., 2007). Demand for new efficient methods for detection of virus particles has resulted in the development of various electrochemical nucleic acid biosensor methods.

Kara et al. (2007) developed a direct label-free electrochemical genosensor to effectively optimize the effect of the probe sequence relative position in an amplicon associated with hepatitis B virus. Li et al. (2007) developed an electrochemical DNA biosensor method using a novel hybridization indicator, bis (benzimidazole) cadmium (II) dinitrate [$Cd(bzim)_2(NO_3)_2$], to effectively detect a short DNA sequence associated with hepatitis B virus, and the detection range and limit were $1.49 \times 10^{-7}$ M to $1.06 \times 10^{-6}$ M and $8.4 \times 10^{-8}$ M, respectively. Tran et al. (2011) developed a chitosan/$Fe_3O_4$ nanoparticle based electrochemical sensor device with a higher electron transfer rate and enhanced sensitivity to effectively detect the presence of human immunodeficiency virus-1 with acceptable stability and good reproducibility. Lin et al. (2009) developed a poly-crystalline silicon nanowire field-effect transistor-based sensor to effectively detect the DNA of high pathogenic avian influenza virus strains H5 and H7.

NOVs are considered to be the most common non-bacterial causes of gastroenteritis, constituting about 50% of all gastroenteritis outbreaks worldwide. Single-stranded RNA NOV is highly contagious with an infectious dose of less than 100 viral particles. Surface plasmon resonance (SPR) biosensor techniques produce significant results for the rapid detection of small molecule toxins, protein toxins, and bacteria. Recently, Yakes et al. (2013) reported a SPR biosensor technique, which efficiently detected the presence of intact viral particles of food matrices with a detection limit of about $10^4$ $TCID_{50}$ feline calicivirus /mL from purified cell

culture lysates, where $TCID_{50}$ is the measure of infectious virus titer. This endpoint dilution assay quantifies the amount of virus required to kill 50% of infected hosts or to produce a cytopathic effect in 50% of inoculated tissue culture cells. Viruses can be used as good substrates for developing a real-time sensor methodology for selective targets under a variety of adverse conditions.

***Immunological Detection Methods***

Nowadays, immunological detection methods using antibodies have been successfully applied in various fields for detection of bacterial cells, spores, viruses, and toxins (Iqbal et al., 2000). As bacterial cells often undergo physical changes, the influence of stress on antibody reactions should be thoroughly examined in order to ensure the reliable detection of foodborne pathogens using antibody based immunological methods (Hahm and Bhunia, 2006).

To date, a number of antibody based methods are available for immunodetection, including enzyme immunoassay, enzyme linked immunosorbent assay (ELISA) (Bennett, 2005; Palumbo et al., 2003), flow injection immunoassay (Abdel-Hamid et al., 1999), bioluminescent enzyme immunoassay (Valdivieso-Garcia et al., 2003), enzyme-linked immunomagnetic chemiluminescence (Gehring et al., 2006), immunomagnetic separation (Liu et al., 2015), immunoprecipitation assay (Feldsine et al., 1997), western blot assay (Oldal et al., 2014), and technically modified western blot assays such as line immunoassay and recombinant immunoblot assay (Ali et al., 2015). Efficacy of ELISA has been confirmed as an important alternative for the detection of viral antigens with confirmed detection of NOV from stool samples (Burton-MacLeod et al., 2004). Although ELISA kits provide efficient detection of viral antigen particles without any complex methodology, they show less detection potency as compared to RT-PCR

detection methods (Burton-MacLeod et al., 2004). In addition, a combination of immunological molecular techniques such as PCR-based immunodetection was shown to have remarkable efficacy for pathogen detection. Musiani et al. (2007) developed a PCR-ELISA based competitive assay for efficient quantitative detection of PCR products. Competitive PCR-ELISA assays have been used for quantitative and standardized detection of parvovirus B19. Furthermore, a surface modified microfluidic system to perform rapid ELISA was also demonstrated for the detection of dengue virus in 30 min (Weng et al., 2011).

In addition, Kosack et al. (2014) developed an immune-flow rapid immunochromatographic assay to detect HCV with good detection sensitivity. Kang et al. (2014) developed a rapid diagnostic test using anti-hemagglutinin monoclonal antibodies specifically targeting H7 in an immunochromatographic assay system for effective detection of avian influenza A (H7N9) virus with a detection limit of 103.5 PFU/mL. Further, Jin et al. (2014) developed a colloidal gold immunochromatographic assay (GICA) for detection of influenza A (H7N9), which and comparable to that of RT-PCR and viral culture assays. GICA showed increased sensitivity and specificity of 91.67% and 82.03%, respectively, for samples collected in the period from 8 to 21 days after contacting with poultry as compared to virus culture assay (Jin et al., 2014). Zhang et al. (2014) tested the activity of various monoclonal antibodies against different influenza viruses in a direct ELISA following the selection of specific antibodies for specific influenza virus based on the performance in the direct ELISA and used to develop a highly sensitive europium nanoparticles based immunoassay (ENIA) for the detection of influenza A/B virus antigen in clinical specimens. The ENIA demonstrated sensitivities of 90.7% for influenza A virus and 81.80% for influenza B viruses compared to those for an in house

reverse transcription-PCR assay in testing of influenza-positive clinical samples (Zhang et al., 2014).

Nowadays, nanoparticle based methods are effectively used for accurate detection of chemical contaminants, viruses, and foodborne pathogens (Tran et al., 2011). These devices utilized nano scaled particles, which attach to pathogens or other contaminants, facilitating selective identification by fluorescence or magnetic devices (Lin et al., 2009). The advantage of these techniques is that they utilize a single sensor and provide a huge range of pathogen detection. Currently, research on nano sensors is focused on two areas: i) development of easy-to-use rapid biosensors for diagnostic detection of pathogens/contaminants in foods and their surrounding environments and ii) incorporation of nano-sensors into food packaging materials for tracking, safety, and biosecurity purposes (Lin et al., 2009). Research into these technologies is likely to continue due to the need to maintain food quality during transportation.

Liposomes tagged with bio recognition agents such as DNA probes, gangliosides (Ahn-Yoon et al., 2004), and antibodies (Shukla et al., 2011; Shukla et al., 2016) are used as signaling reagents in amplification, with significant potential for instantaneous signal acquisition (Ahn-Yoon et al., 2004). Application of liposomes usually results in the removal of non-specific binding, promotion of specific binding, and enhanced encapsulation efficiency and stability (Edwards et al., 2012). Liposomes as bilayer phospholipid components are frequently used in pathogen diagnostics due to their several advantages over culture-dependent traditional detection methods (Shukla et al., 2011). In addition, novel biological elements have been employed in microfluidic and lateral flow assays, such as ganglioside incorporating liposomes, for the easy detection of virus pathogens. Connelly et al. (2012) developed a microfluidic pre-concentration

method coupled with liposome based signal amplification to efficiently detect enteric viruses in environmental water samples. This study utilized surface modified fluorescent streptavidin conjugated SRB encapsulated liposomes with anti-FCV monoclonal antibody which served as a signal generator for detecting virus particles (Connelly et al., 2012). Nowadays, immunoassay sandwich ELISA techniques coupled with antibody tagged liposomes are used for easy detection of virus particles, which is the key prerequisite for using such integrated devices in virus detection of environmental water samples (Connelly et al., 2012). Further, Connelly et al. (2012) developed an electrochemical liposome based assay by directly injecting virus-liposome-bead detection complexes towards a magnet. The integrated current signals from the lysis of captured liposomes resulted in the detection of viral titer in the environmental sample with a detection limit of $1.6\times10^5$ PFU/mL for feline calicivirus.

Further, Egashira et al. (2008) developed a rapid and highly sensitive detection method by combining electro chemiluminescence with an immunoliposome encapsulating a Ru complex. Under optimum measurement conditions, hemagglutinin molecules of influenza virus were determined in a concentration range of $3 \times 10^{-13}$ to $4 \times 10^{-11}$ g/mL, which suggested that $6 \times 10^{-19}$ mol/50 µL could be considered the lowest detectable concentration of viral hemagglutinin molecules by this method. These findings confirmed that the method with high detection sensitivity at the attomolar level could be applicable for detecting trace amounts of various proteins in influenza virus. Damhorst et al. (2014) also developed an ELISA-inspired lab-on-a-chip strategy with electrical sensing technique for the detection of biological entities after tagging with ion-encapsulating liposome particles and ion-release impedance spectroscopy measurements. In this method, ion-encapsulating dipalmitoylphosphatidylcholine liposomes are

functionalized with antibodies and are stable in deionized water yet permeabilized for ion release upon heating, making them ideal reporters for electrical biosensing of surface-immobilized antigens. The authors demonstrated quantification of these liposomes by real-time impedance measurements, as well as qualitative detection of viruses as a proof-of-concept toward a portable platform for viral load determination which can be applied broadly to the detection of pathogens and other biomolecules (Damhorst et al., 2014).



***Miscellaneous Detection Methods***

A plethora of molecular diagnostic methods have been designed and used for the detection and genotyping of HCV infection. Furthermore, the application of these assay methods may be limited regarding their ability to detect and simultaneously identify the specific HCV genotypes. Nyan and Swinson (2016) developed a one-step reverse transcription loop-mediated isothermal amplification method for the detection of HCV. The assay demonstrated a sensitivity of 91.5% and specificity of 100%. Rapid naked-eye detection of HCV infection was facilitated by observation of an intense fluorescent glow of amplified targets under UV illumination (Nyan and Swinson, 2016).

In addition, HEV has become a well-known zoonotic enteric pathogen and circulated widely through inter human-animal-water-food chain. Recently, Gao et al. (2016) reported one-step single-tube RT-LAMP assay for rapid detection of HEV contamination in shellfish. The amplification took 60 min under the isothermal condition (63°C) and was visually evaluated by staining about 1 h. The sensitivity results of RT-LAMP assay showed that the detection limit of RT-LAMP reached about $10^1$ copies/μL of target RNA (Gao et al., 2016).

Further, quartz crystal microbalance (QCM) is a widely used biosensing tool due to its simplicity and sensitive response in the oscillation frequency to surface changes of the crystal. QCM sensors have been used for the detection of avian influenza virus based on antibody-antigen interactions (Li et al., 2011) and aptamer incorporated hydrogels (Wang and Li, 2013). The results were obtained in 30 min and were faster than the antibody based counterpart. In addition, field effect transistor (FET) detectors are also good candidates for a detection platform with high sensitivity. Hideshima et al. (2013) developed a attomolar detection method for the detection of hemagglutinin particles from influenza viruses, human H1, and avian H5 using a glycan-immobilized FET biosensor, where small ligand glycans were immobilized on the FET device, thus making effective use of the charge-detectable region for FET-based detection in terms of Debye length. This method gave an advantage on the highly sensitive detection of viral proteins using FET detector, and the sensitivity of detection method based on binding between hemagglutinin and sialic acid containing carbohydrates was brought down to attomolar (Hideshima et al., 2013). Kim et al. (2013) reported that addition of hydrophobic passivation layer to the popularly used hydrophilic passivation layer of FET sensors can increase a 100-fold improvement in the detection sensitivity, achieved for antibody-antigen based detection, suggesting that higher sensitivities could be realized if these two FET techniques are incorporated into the same device.

Apart from liposome-based typical immunological detection, there are several reports on liposome based non-immunological detection assays for the detection of virus particles. To elucidate the molecular mechanisms of detection and transmission of influenza viruses in different host species, such as human and birds, Hidari et al. (2007) observed the binding

properties of sialic acid-containing liposomes recognized in human and/or avian influenza viruses which were characterized by SPR method. The SPR coupled with immobilized sialic acid containing liposomes offers a limit of detection (LOD) down to 0.1 pM-$6\times10^4$ viruses/ μL) (Hidari et al., 2007), and a very similar LOD for analysis of influenza A virus was also achieved with SPR based on a chip immobilized with bovine brain lipid containing sialo-glycolipids (Critchley and Dimmock, 2004).



**RESEARCH NEEDS AND FUTURE HYPOTHESIS**

The number of well-designed studies on detection of various foodborne pathogens, including virus particles in fresh produce, should be increased. Moreover, methods for isolation of virus particles should be designed based on their statistical relevance, consistency, treatment strategies, laboratory test methods, and data analysis profile, and the results of negative consequences should be reported.

Further, we previously developed various liposome-based immunoassays for the detection of different bacterial strains such as liposome based immunochromatographic strip assay for detection of *Salmonella* (Shukla et al., 2011), liposome based immunomagnetic assay for detection of *Salmonella* and *Cronobacter sakazakii* (Shin and Kim, 2008; Shukla et al., 2016), a combined immunomagnetic separation and test strip liposome assay for detection of *E. coli* O157:H7 (Kim et al., 2003), and a liposome based immunochromatographic test strip for detection of *Salmonella* in contaminated tomato samples (Shukla et al., 2012; Shukla et al., 2014). In our previous works, we reported polyclonal antibody production, purification, and applicability with liposome-based assays. To date, no research is available on liposome based assays for detection of foodborne viruses. Thus, a specific foodborne anti-virus antibody should

be made in order to develop a liposome based detection system to analyze virus contamination in food products. A hypothesis of predicted model of liposome-based immunochromatographic strip for viral detection is summarized in Figure 3. Briefly, the assay will involve an antigen capture zone (test line) in the nitrocellulose membrane strip, which is exposed to the target virus particle in a solution containing immunoliposome. Liposomes are sulforhodamine B (SRB) encapsulated and tagged with anti-virus antibody, which are specific for the binding of specific virus particle, in the presence of virus particle. Then, these immunoliposomes and a virus particle complex migrate through the test strip by capillary action and subsequently bind to the test line of the membrane and produce a purple color band. However, some amount of immunoliposomes, which is not bound with virus particle at the test line continues to migrate and bind to the control line of membrane to develop the purple color band, and shows positive results for the presence of virus particles (Figure 3). While in the absence of virus particle in test samples, immunoliposomes are not able to bind to test line, thus they migrate and bind at the control line on test membrane and develop the purple color line at the control line only, and confirm negative results for virus particle detection (Figure 3).

In addition to this strategy, there might be another strategy to develop combined assay of liposome and immunomagnetic nano particles for the sensitive detection of virus particles as summarized in Figure 4. The assay procedure can be divided into the following three steps: immunomagnetic concentration and separation of target virus particle, reaction of immunoliposome particles with virus particle cells attached to immunomagnetic nanoparticles, and fluorescence signal generation (Figure 4). In the first stage of assay development, the target virus particle will be concentrated and separated using anti-virus antibody-conjugated magnetic

nanoparticle complexes via the magnetic field of a simple magnet system (Figure 4 a-c). Following this stage, the concentrated target virus will be combined with immunoliposome particles (anti-virus antibody -conjugated liposomes), resulting in a heavier complex comprised of viral particle attached to immunoliposome particles (Figure 4d). Because this stage also requires the removal of free immunoliposomes particles, the complexes would be again passed through a magnetic field. Next, to generate detectable signals from the immunocomplexes (i.e., the immunoliposome-virus particle-immunomagnetic nanoparticles), n-octyl-β-D-glucopyranoside (OG) could be used as a detergent to lyse the liposome particles. The addition of 30 mM OG to the immunocomplexes will result in lysis of the liposomes and release fluorescence dye, SRB (Figure 4e). The fluorescence signals will be compared against the signal generated by a blank sample without virus particle. SRB fluorescence following liposome lysis could be measured at an excitation wavelength of 550 nm and an emission wavelength of 585 nm (Figure 4f). In the near future, studies should attempt to confirm the practical applications of liposome based virus detection assays in various food samples contaminated with foodborne viruses.



**CONCLUSION**

From an epidemiological point of view, the most relevant viral pathogens found in water are HAV, HAE, and gastroenteritis viruses, which include rotaviruses, caliciviruses, Norwalk-like viruses, astroviruses, and enteric adenoviruses. Moreover, handling difficulties and technical issues have restricted research for testing and detecting viruses in various food samples to sophisticated facilities and well-trained personnel only. Thus, further studies are needed to estimate the burden and cost of illness due to foodborne viral infections with special emphasis on

determining the burden of illness in the elderly so as to provide baseline data for future intervention and prevention programs on a range of viruses. To ascertain such parameters, better surveillance of illnesses is needed along with advanced tools and molecular biology techniques for tracing viruses throughout the food chain and human populations. Rapid detection methods and typing of foodborne viruses should be developed, and convenient exchange of typing information between laboratories and countries should be encouraged by evaluating currently available virus detection techniques in practical applications. Standardization and feasibility of such virus detection methods for screening food and environmental samples should be well studied. New insights and interpretations should be made by studying the mechanisms of emergence of epidemic virus strains in association with animal viral infections. In conclusion, innovative approaches are being made for the detection of foodborne viruses in food products, particularly relating to harmonization of current methodologies, which may provide new insights into research and development strategies on the current status of virus research.

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**Table 1** Update on important and recent outbreaks of foodborne viral diseases

| Virus strain | Country/Location | Year | No. of ill cases | Associated food | Reference | Causality |
|---|---|---|---|---|---|---|
| Hepatitis A virus | United States | 2003 | - | Green onion | CDCP, 2003 | None |
| | United States | 2003 | 601 | Green onion | Wheeler et al., 2005 | 3 death |
| | South Korea | 2008 | - | Uncooked lettuce/ carrot | Yoon et al., 2009 | None |
| | Australia | 2009 | >70 | Tomatoes (semidried tomatoes) | DHVSA, 2009 | None |
| | France | 2010 | 59 | Semidried tomatoes | Gallot et al., 2011 | None |
| | Netherland | 2010 | 13 | Semidried tomatoes | Petrignani et al., 2010 | None (One acute liver failure) |
| | England | 2011 | 237 | Semidried tomatoes | Carvalho et al., 2012 | None |
| | Italy | 2013-2014 | 1,102 | Frozen berries | Severi et al., 2015 | 2 deaths |
| Norovirus | Finland | 2006 | >400 | Raw vegetable | Makary et al., 2009 | None |
| | United States | 2001-2008 | 2,922 | - | Hall et al., 2012 | None |

| | | | | | | |
|---|---|---|---|---|---|---|
| | South Korea | 2008 | 131 | Salad/ school canteen food | Yu et al., 2010 | None |
| | Europe | 2010 | - | Lettuce | Ethelberg et al., 2010 | None |
| | Finland | 2009 | 200 | Raspberries | Maunula et al., 2009 | None (acute gastroenteritis) |
| | China | 2012 | 30 | Food and Water | Guo et al., 2014 | None (acute diarrhea and fever) |
| | China | 2013 | 87 | (Bread from unlicensed bakery) | Guo et al., 2014 | None (Severe gastroenteritis) |
| | United States | 2016 | 700 | Restaurant food | FSN, 2016 | None |



 

**Table 2** List of recently developed methods for detection of viral contamination

| Method | Category of detection method | Sample analyzed | Tested virus strain | Detection limit | Sensitivity reported | Reference |
|---|---|---|---|---|---|---|
| RT-PCR | PCR based methods | Fresh berries, vegetables (lettuce, tomato, radishes) | Hepatitis A virus, Norwalk-like virus | $5\times10^{1}$ PFU/100 g | Not reported | Dubois et al., 2002 |
| Cationally charged magnetic particle-based RT-qPCR | | Lettuce, strawberries, green onion | Hepatitis A virus, Norwalk-like virus | $10^{2}$ PFU/25 g | Not reported | Papafragkou et al., 2008 |
| Positively charged membrane/integrated cell culture | | Iceberg lettuce | Hepatitis A, Norwalk-like | 3 log RNA copies | Not reported | Hyeon et al., 2011 |

| | | | | | | |
|---|---|---|---|---|---|---|
| based RT-qPCR | | | virus | | | |
| Duplex qRT-PCR | | Raspberries | Hepatitis A virus, Norwalk-like virus | 50 PFU/25 g raspberries, 100 PFU/ 1.5 L bottled water | High sensitivity | Sandra et al., 2010 |
| Total nucleic acid extraction with RT-qPCR | | Fresh produce (green salad) | Hepatitis A virus | $3\times10^2$ PFU/25 g | 85.09% | Hida et al., 2013 |
| Rapid single tube method by nested RT-PCR | | Artificially spiked green onions | Hepatitis A virus, Noro virus | 0.1-1 PFU for green onions/25 g | 90.04% | Hu and Arsov, 2014 |
| RT- PCR based rapid detection method | | Raspberries and stool sample | Norovirus | - | - | Le Guyader et al., |



 

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | 2004 |
| Rapid loop-mediated reverse transcription isothermal amplification assay | | Cell culture | Hepatitis C virus | $10^5$--0.1 IU/per reaction | 91.5% | Nyan and Swinson, 2016 |
| Reverse transcription-loop-mediated isothermal amplification (RT-LAMP) assay | | Shellfish | Hepatitis E virus | $10^1$ copies/μL of target RNA | High sensitivity | Gao et al., 2016 |
| Immunochromatographic assay system | Immuno chro-matographic assay | Clinical samples | Avian influenza A (H7N9) virus | $10^{3-5}$ PFU/mL | 61.5% | Kang et al., 2014 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Colloidal gold immunochromatographic assay | | Clinical samples | Influenza A (H7N9) | 10 ng/mL | 91.67% | Jin et al., 2014 |
| Immuno-flow hepatitis C virus (HCV) rapid immunochromatographic test | | Clinical samples | Hepatitis C virus | - | 99.0% | Kosack et al., 2014 |
| Immunochromatographic test | | Clinical specimens | Enterovirus | - | 84.0% | Huang et al., 2013 |
| Immunomagnetic capture RT-PCR | Immuno-magnetic assay | Cell culture | Hepatitis A VIRUS, rota virus, enterovirus | 0.1-1.0 PFU | Not reported | Casas and Sunen, 2002 |
| Lectin-linked immunomagnetic bead assay | | Cell culture | Hepatitis A virus | $10^4$ $TCID_{50}$/mL | Not reported | Ko et al., 2014 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Microfluid immunomagnetic separation | | Clinical specimens | Influenza virus | - | 84.8% | Hung et al., 2013 |
| Micro-total-microfluidic pre-concentration coupled to liposome based assay | Liposome- based immuno assay | Cell culture, water sample | Enteric viruses | $1.6\times10^{5}$ PFU/mL | Not reported | Connelly et al., 2012 |
| Electrochemiluminescence Sensor with an Immunoliposome | | Cell culture | Influenza virus | $3\times10^{-13}$ to $4\times10^{-11}$ g/mL | High sensitivity | Egashira et al., 2008 |
| Liposome-based ion release impedance sensor | | Cell culture | Human immuno-deficiency virus | Qualitative detection | - | Damhorst et al., 2014 |
| Europium nanoparticle | Nanoparticle- | Clinical samples | Influenza A and | $10^{4-8}$ $TCID_{50}$/ | 90.7% and 81.80% | Zhang et al., 2014 |

| | | | | | | |
|---|---|---|---|---|---|---|
| based immunoassay | based immuno assay | | influenz a B virus | mL | | |



 

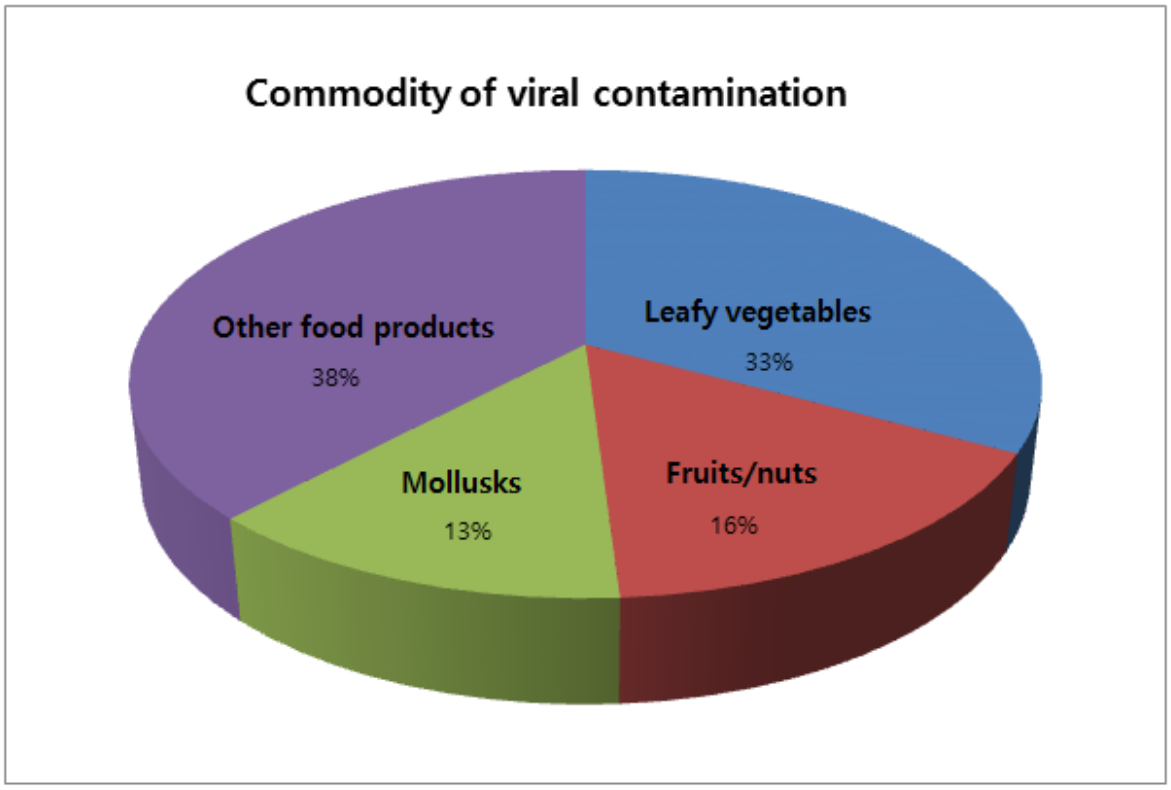


**Figure 1** Commodity of contamination reported in viral outbreak in different food matrixes (adopted from Hall et al., 2012).

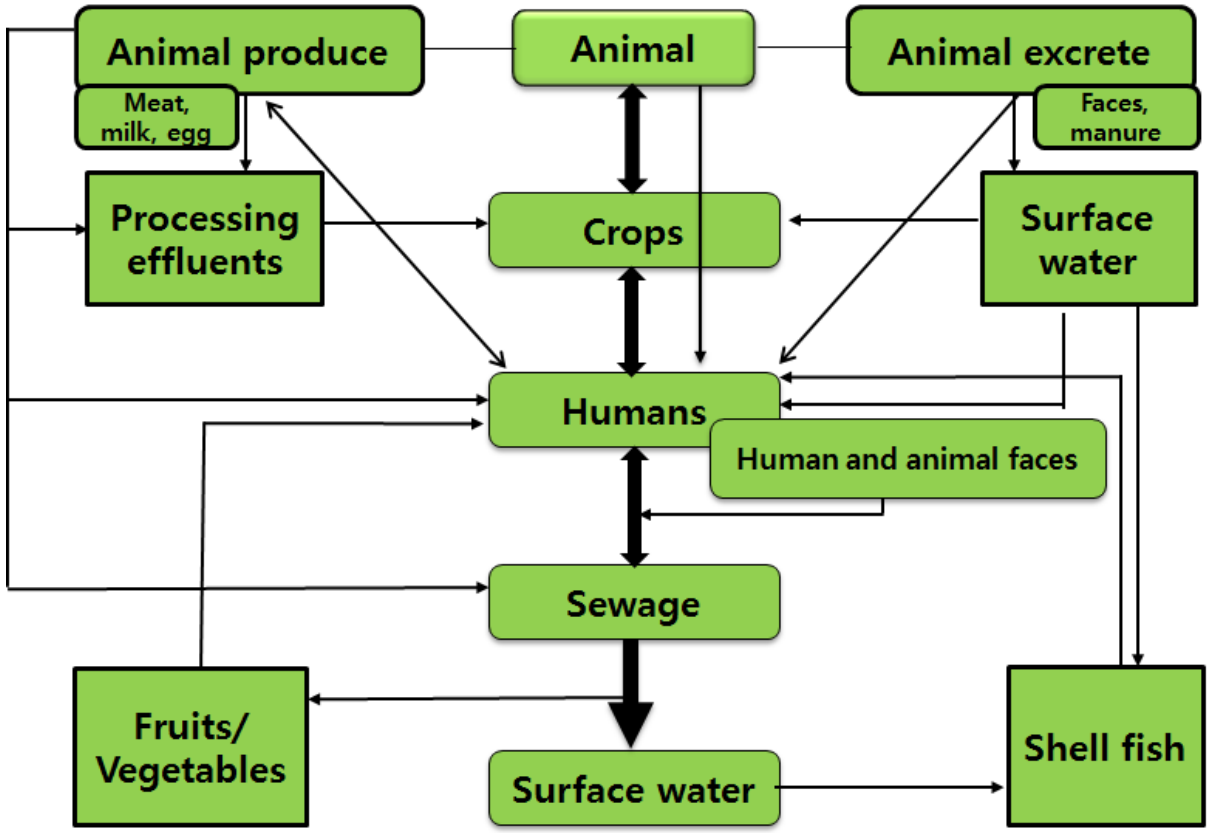


**Figure 2** Routes of transmission/contamination for viruses from animal origin and foods to humans.

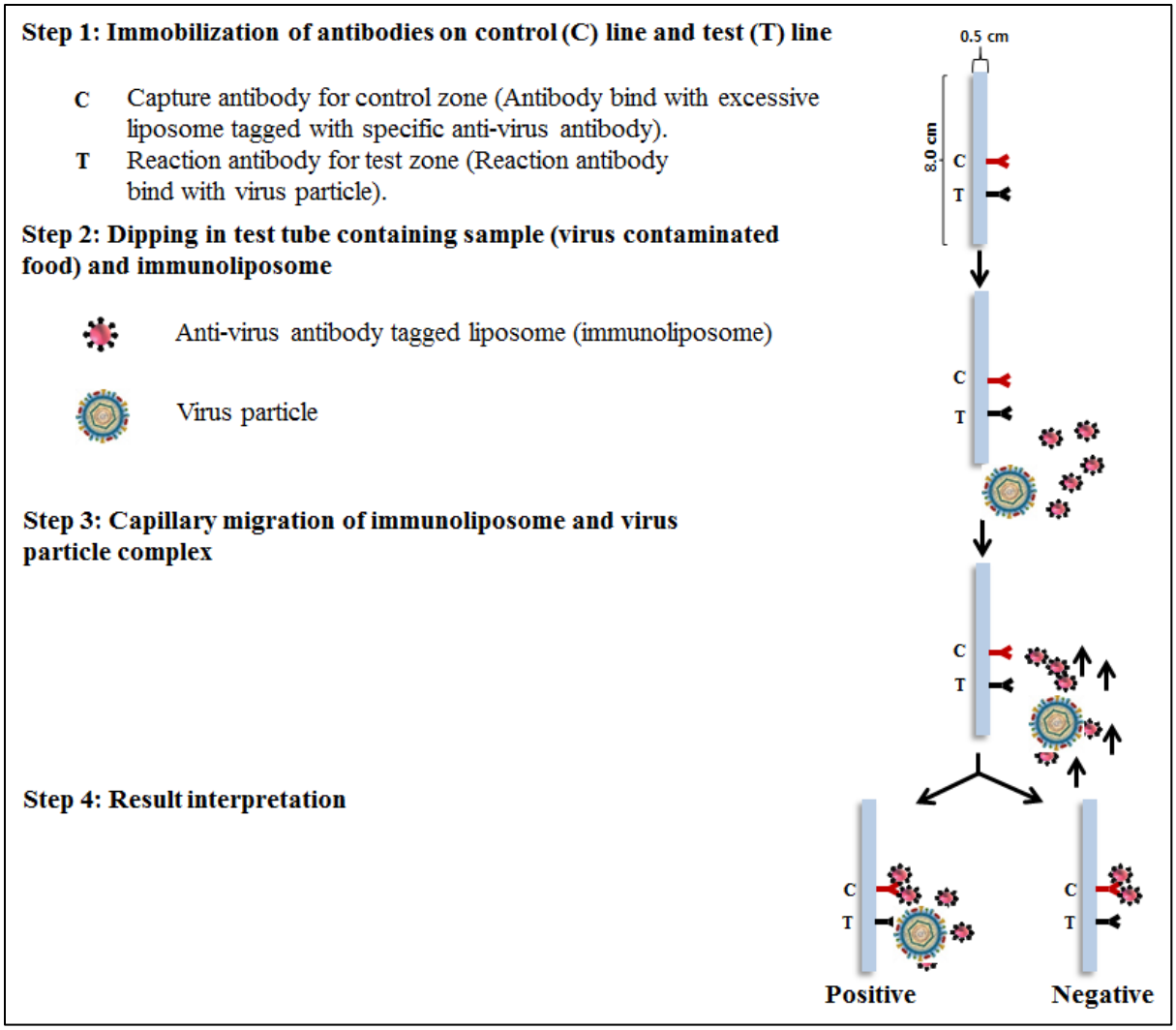


**Figure 3** Research theme for developing liposome based detection method for specific food-borne virus contamination in food products (Hypothesized from Shukla et al., 2011).

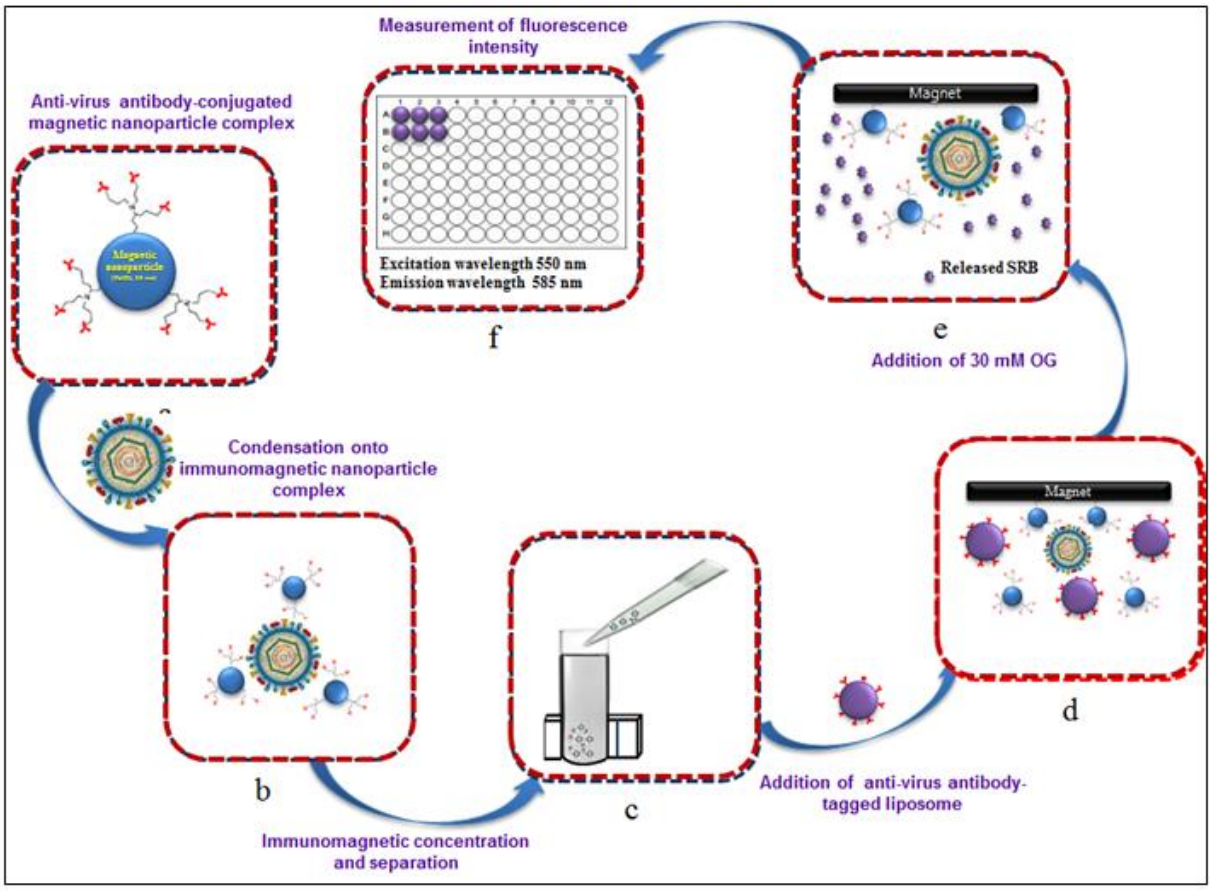


**Figure 4** Strategy for developing immunoliposome and immunomagnetic particle based sensitive detection for virus particles (Hypothesized from Shukla et al., 2016).