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Preparedness for the transmission of pandemic viruses in the food chain

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ABSTRACT

Governments and the food industry make major efforts to ensure food safety throughout the global supply chain and support food availability. Experiences with Coronavirus disease 2019 (COVID-19) have re-emphasized the need for preparedness in many sectors, including the food sector. This position paper analyzes the potential introduction and transmission of pandemic viruses via the food chain and hypothesizes which new food safety issues could arise. Two scenarios, a gastrointestinal virus and a respiratory virus, were explored. Possible risks and economic costs of introduction and transmission, regulatory and analytical needs, and control strategies associated with such scenarios are described. Overall, if a pandemic virus associated with the food chain was to occur, our preparedness is currently lacking given our potentially limited knowledge of introduction and transmission pathways, as well as access to methods to detect the viral presence and infectivity and model the transmission of the pathogens, even though the economic and societal impact of such a scenario is likely extensive. The food and fomite component could be easily neglected or underestimated in a future pandemic. On the other hand, better tools to prove the lack of food chain transmissibility of a pandemic virus could also prevent unnecessary economic losses across the sector. In the event of a foodborne pandemic virus, food safety testing would provide a clear purpose to detect deviating batches, obtain monitoring data, and assess compliance to hygiene criteria; however, providing complete safety through enforcement criteria is demonstrated to be economically unfeasible; therefore, other control interventions will be needed. These messages are important for food business operators and governments to understand the possible analytical needs, opportunities, and caveats for food safety testing. Narrowing the knowledge gaps on introduction and transmission, and improvement of analytical feasibility is required to benefit our preparedness against the emergence and spread of future foodborne pandemic pathogens.

1. Introduction

According to the World Health Organization, as of February 2023, there are over 750 million confirmed cases and 6.8 million deaths resulting from Coronavirus disease 2019 (COVID-19) (World Health Organization, 2023). COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic virus characterized by efficient person-to-person transmission, initially little or no immunity in populations, and risk of severe disease. For more than two years, COVID-19 has impacted our socio-economic system. The food sector has faced considerable challenges in production, distribution, processing, trade, and consumer demand. The latter was seen globally with stockpiling and panic-buying of household food supplies and the closure of restaurants and food services. Food safety and food availability must, however, always remain guaranteed. Consequently, governments and the food industry have gone through major efforts to ensure food safety throughout the global supply chain and to support food availability.

In the COVID-19 pandemic, the transmission of SARS-CoV-2 via food has been reported to be unlikely (González et al., 2021; Rose-Martel et al., 2021). Nonetheless, the COVID-19 pandemic has placed pressure on the food system and globally affected food security, e.g., by disruptions in the workforce and supply chains and travel- and trade restrictions (Bron et al., 2021). Experiences with COVID-19 re-emphasize the need for preparedness in many sectors, including the food sector. The possibility of the transmission of a pandemic virus via food needs to be considered. Foods that are handled or traded raw are associated with

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various viral food-borne illnesses (Bosch et al., 2018). If food products or packaging were to play a role in spreading a pandemic virus, analytical methods would then be needed to detect viruses. Alongside this need, it is relevant to evaluate the transmission routes for new sources of viral infection, how the spread of these viruses occurs, and to design cost-effective control measures. These above-mentioned knowledge elements require further actions to better prepare for a scenario where pandemic pathogens are transmitted via food supply chains. For this, several questions arise about a possible food-borne pandemic occurring in our food supply chain:

- What is known about the role of food and the food chain in introducing and transmitting potentially highly pathogenic viruses into the human population?
- How could scenarios look like in which, next to person-to-person spread, food plays a relevant role in the transmission of a pandemic virus?
- How well prepared is our current food safety system, including regulatory bodies and current guidelines, for such a situation?
- Which analytical methods are needed to investigate and confirm the infectivity of pandemic foodborne viruses?
- What would be the economic impact on the food system?

The aim of this study is to evaluate the potential introduction and transmission of pandemic viruses via the food chain, hypothesize consequences for food business operators and assess the economic impact that could arise if a food-borne transmissible pandemic virus was to occur. We illustrate the impact of a pandemic that also transmits across the food chain with two scenarios, a pathogenic gastrointestinal virus with increased virulence and a pathogenic respiratory virus with gained stability, and their consequences for hygiene codes. To assess the potential economic effects and societal costs associated with these scenarios, we hypothesized a pandemic occurrence in two vulnerable food chains – the strawberry chain and the salmon chain. The results of this study help food-business operators and governments consider the possible risk and impact of pandemic viruses being introduced and transmitted via our food system and the regulatory and analytical needs, as well as control strategies associated with such scenarios.

2. Role of food in the introduction of viruses into the human population

The scientific community closely watches the emergence and spread of several viruses with potential pandemic properties and their impact on public health. The avian Influenza A virus is considered a global health threat, causing recurring pandemics in 1918, 1957, 1968, and 2009 (Harrington et al., 2021). The year 2022 has also seen an alarming number of Influenza A outbreaks in poultry farms in Europe (Adlhoch et al., 2022), emphasizing the importance of pandemic preparedness against high-risk viruses (Naguib et al., 2020). Recent viral pandemics such as Influenza A H1N1 and SARS-CoV-2 have been characterized by person-to-person respiratory transmission. It is, however, difficult to precisely determine the food and fomite transmission component compared to respiratory transmission due to an incomplete understanding of the adsorption and transfer properties of viruses, as well as challenges in sampling and quantifying infective viruses from surfaces including foods (Castano et al., 2021).

Even though it is probably not possible to predict the exact origin and impact of a future pandemic, substantial health, economic and societal consequences are expected, as shown by previous pandemic viruses like SARS-CoV-2 (Panneer et al., 2022). In our study, a literature review was performed (details in Supplementary materials: Methods A) to assess how food has contributed to the introduction of new viruses in the human population and which pandemic viruses could have the potential to spread across the food chain. Food can play distinctive roles in the emergence of viruses, including their spillover to the human population. Food can mediate viral spillover either through direct ingestion of virally contaminated food but also via on-farm contact with the husbandry or game. For example, the Nipah virus has spilled over from bats to pigs to humans in an outbreak in Malaysia through close contact with the pigs rather than the consumption of porcine meat (Chua, 2003; Parashar et al., 2000). In Bangladesh, there have been seasonal Nipah virus outbreaks in the human population caused by the consumption of raw date palm sap contaminated with bat secretions during winter (Hassan et al., 2022). SARS-CoV-2 has most likely emerged in a seafood market in Wuhan, China (Worobey et al., 2022), while SARS-CoV-1 likely emerged through the ingestion of Chinese ferret badgers, raccoon dogs, or Himalayan palm civets sold as food (Maske et al., 2021). Avian influenza has very occasionally spread to humans through live poultry at markets and duck farms (Cáceres et al., 2021) and through wild bird pet trade (Dudley, 2008). Intensive livestock production possibly facilitated Reston ebolavirus spillover from livestock in the Philippines and Marburg virus and Ebola virus in sub-Saharan Africa (Glennon et al., 2018). The Hepatitis E virus has been described as a risk for humans who consume game meat (Hedman et al., 2020) and porcine meat (EFSA Panel on Biological Hazards (BIOHAZ) et al., 2017). Infection with rabies lyssavirus and parapoxvirus has occurred after direct contact with hunted wild animals (Hedman et al., 2020). Hunting and consumption of non-human primates is a public health concern due to close contact between humans and animal carcasses and raw meat (Devaux et al., 2019). Finally, bushmeat is considered one of the primordial risk factors associated with the Hendra virus and Nipah virus spillover to human populations in Africa (Mbu'u et al., 2019; Pernet et al., 2014; Weiss et al., 2012). Collectively, these examples highlight the substantial role of food in introducing viruses into the human population. Zoonotic spillover is proposed to occur most commonly through direct contact with husbandry animals that are grown for food rather than the consumption of animal foods (Ellwanger & Chies, 2021). However, surface-mediated spillover of viruses through the direct consumption of food did also occur for Nipah virus through bat guano after ingestion of date palm sap. Although serological and epidemiological links have identified the source of the spillover in the last example, it remains scientifically challenging to provide a specific likelihood for this mode of transmission across all spillover events.

In summary, a body of literature illustrates that the food chain is a mediator for spill-over events of viruses. Many of these viruses (i.e., Nipah, Hendra and Marburg virus, Ebola virus, SARS and MERS) are among those that are prioritized by WHO for their epidemic potential (World Health Organization, 2022b) and ranked high for their zoonotic spillover potential (e.g., Ebola, Seoul, Nipah, Lyssa, Hepatitis E and Marburg virus and SARS-CoV-1 and 2) (Grange et al., 2021). The historical role of food in the emergence of viruses, together with their estimated epidemic potential, sketches plausible scenarios for the involvement of the food chain in a pandemic virus outbreak. When a food (chain) related spillover event occurs, this could catalyze a pandemic where either food can continue to play a role or where it becomes a less relevant vehicle or route. The likelihood of the food itself becoming a major transmission route in a scenario where a new pandemic virus emerges from the food chain is yet unknown.

3. Role of food in the transmission of a pandemic virus

The WHO estimated that yearly almost one in ten persons in the world fall ill after consuming contaminated food (World Health Organization, 2017). Most frequently, food-borne illness is caused by diarrheal disease agents, although over 200 different diseases can be transmitted through food. Previous food-borne viral epidemics have not exhibited the level of transmissibility required to be classified as a pandemic. Most historical pandemics have been characterized by respiratory transmission. At the same time, in current pandemic investigations, the food-borne transmission component is often poorly defined and sometimes neglected (Otter et al., 2016).

In our study, we performed a second literature study (described in Supplementary materials: Methods A) to investigate known foodborne or fomite transmission of respiratory viruses. We investigated in which environments transmission of surface stable respiratory viruses has occurred, what percentage of transmission was mediated by surfaces rather than aerosols, and whether gastrointestinal infection occurred in these instances. During the SARS-CoV-2 pandemic, no evidence was found of virus transmission through the soil, dust, and clean water environments (Shao et al., 2021) or transmission through infected animals kept or caught for human consumption. However, the virus can remain infectious for two days in uncooled water (La Rosa et al., 2020) and multiple days on surfaces such as plastics, metals, and clothes (Aboubakr et al., 2021), while SARS-CoV-1 and MERS-CoV have remained infectious on frozen foods for years (Adelodun et al., 2021). In addition, SARS-CoV-2 nucleic acid persistence was demonstrated on frozen cod packages (Liu et al., 2020).

Evidence for SARS-CoV-2 transmission via surfaces or food products and packaging remains controversial. In cases where potential surface or food product transmission has occurred (Wang et al., 2022), infected individuals have been in the physical vicinity, making it hard to rule out strictly airborne transmission. No comprehensive method exists to discriminate fecal-oral or surface transmission from direct respiratory transmission to humans in these scenarios (Mbu'u et al., 2019). A quantitative microbial risk assessment (QMRA) study for SARS-CoV 2 estimated that there would be less than 1:10,000 (Wilson et al., 2021) chance of infection after touching a contaminated surface (Edwards et al., 2022). Although the respiratory viruses SARS-CoV-1 and 2, MERS-CoV, and avian influenza are all capable of remaining infectious on fomites for multiple days, contact through contaminated surfaces appears to be a frequent transmission route mainly for avian influenza (L. Guo et al., 2021; Kampf et al., 2020; Otter et al., 2016). Estimating transmissibility through fomites remains challenging, leading to great heterogeneity in transmissibility estimates across different studies (Leung, 2021). The discrepancy between transmission routes is problematic for pandemic risk management, especially when simulation experiments for future pandemics are based on incomplete data or biased models.

Due to challenges in establishing attribution of the surface and food-to-person mode of transmission during viral emergence and pandemics, there is a knowledge gap in the environmental or surface transmission of viruses. As a result, the food and fomite component could be easily neglected or underestimated in the early phases of a future pandemic.

4. Scenarios

If food becomes a vehicle for pandemic viral transmission, the fear of worldwide virus dissemination via food will affect international food trade, asking for additional intervention measures to contain the foodborne viral spread and secure access to food sources. Especially food items that are consumed raw or undercooked, either derived from fresh or frozen food chains with intense manual handling, are prone to the introduction and transmission of human viruses (Bosch et al., 2018).

Gastrointestinal viruses, such as norovirus (NoV), are spread person-to-person via contaminated water and food and after deposition on surfaces and subsequent oral ingestion. The higher environmental stability of gastrointestinal viruses relative to respiratory viruses facilitates this transmission mode. In contrast, respiratory pathogens such as SARS-CoV-2 spread to new hosts mainly via coughing and exhaling saliva and aerosols. Noteworthy for a pandemic virus (PV) is its transmissibility. A foodborne PV would, in addition, need to be exceptionally stable to facilitate a surface mode of transmission. This also includes a continuation of transmission via the person-to-person route once the surface stable PV has been introduced into the human population, as well as transmission by individuals with or without symptoms, notably when working in the food chain. Another threat could be when variants of the PV are present on food or even accumulate in food, e.g., oysters leading to recombination events within the host cells.

In our study, we evaluated the scenarios of (i) an emerging, non-enveloped, gastrointestinal food-borne virus that develops a significant disease burden and (ii) an emerging respiratory virus associated with severe illness that gains the environmental stability of a food-borne virus. The relevance of these two scenarios with two selected exemplary food chains, i.e., strawberry and salmon, is then elucidated.

4.1. Scenario PV1: pandemic transmission of a gastrointestinal virus via food

Of all foodborne viruses, noroviruses are most frequently associated with foodborne viral disease and are the leading cause of gastroenteritis worldwide (World Health Organization, 2015). Humans are most likely the only reservoir for human pathogenic noroviruses (Glass et al., 2009). NoV is transmitted via the fecal-oral route, as well as via ingestion of vomit aerosols, promoted by a sudden onset of vomiting (Zelner et al., 2013). The relative contribution of different transmission routes to the public health risk remains unknown (EFSA Panel on Biological Hazards (BIOHAZ), 2011).

NoV properties such as high environmental persistence due to its small size and lacking virus envelope, the great number of excreted viruses, the high probability of infection per ingested virus particle, and its antigenic variation contribute to the success of NoV as a foodborne pathogen. Despite the great genetic diversity of NoV, genogroup II genotype 4 (GII.4) is responsible for the majority of disease cases with a global spread of GII.4 strains which are periodically emerging and replacing the previous predominant strain (Bull et al., 2010; Lindesmith et al., 2008; Siebenga et al., 2009, 2010). NoV infection is generally mild and self-limiting, but what if a pandemic strain evolves that causes more severe infectious outcomes? In our first scenario (Fig. 1), we elaborate on the consequences of a non-enveloped, gastrointestinal food-borne virus, such as an emerging pandemic NoV strain, with an increased disease burden on food safety management and economic aspects.

4.2. Scenario PV2: pandemic transmission of a respiratory virus via food

We focused on a respiratory virus in our second scenario, as this group of viruses is considered to have the highest pandemic potential due to their efficient person-to-person spread. O'Brien et al. (2021) give an overview of viruses that are known to cause respiratory illness in humans but also have the potential for foodborne transmission. Currently, there is little epidemiological evidence that foodborne transmission of respiratory viruses plays a significant role in virus transmission (O'Brien et al., 2021). However, infectious respiratory viruses with envelope, such as SARS-CoV-2 or avian influenza H5N1, can also cause gastrointestinal symptoms and can be excreted via feces (de Jong et al., 2005; M. Guo et al., 2021). Receptors for cell entry of respiratory viruses, such as SARS, are not only expressed in the respiratory tract but also in the gastrointestinal tract, facilitating potential replication in the intestinal epithelium (M. Guo et al., 2021). In addition, there is growing evidence that certain enveloped respiratory viruses can persist in low pH and digestive juices, potentially by the protection of virus particles from degradation by viscous mucus (Hirose et al., 2017) or food matrices (Han et al., 2019; Harlow et al., 2022).

Next to a potential fecal-oral spread, the transmission of a more environmentally stable respiratory virus may then also occur by contamination of food with respiratory droplets from infected persons. In our second scenario study (Fig. 2), we, therefore, describe an enveloped respiratory virus that evolved into an environmentally stable virus, which is efficiently transmitted via food contaminated by respiratory droplets as well as by fecal contamination.

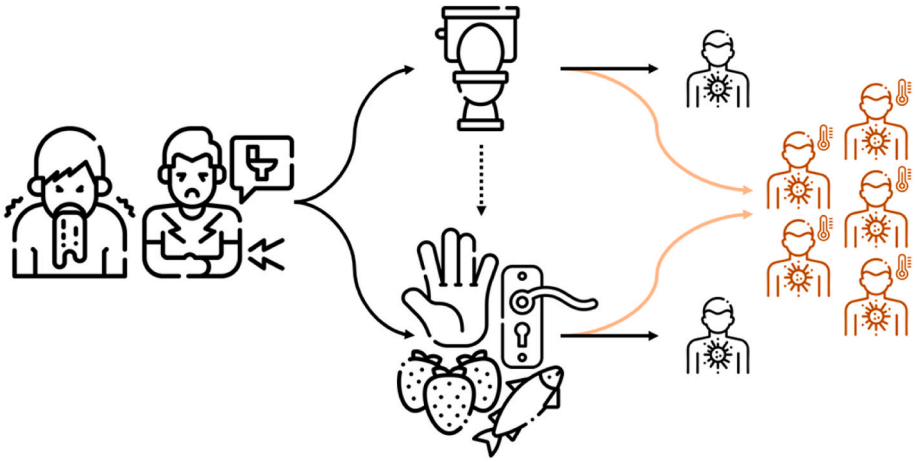

Fig. 1. Scenario PV1: Pandemic transmission of a gastrointestinal virus via food. Transmission of a gastrointestinal virus via fomites and food (current situation, black) and additional transmission of a pandemic gastrointestinal virus, i.e., a virus that has evolved to increase virulence and/or pathogenicity (orange). Image icons designed by Freepik (www.freepik.com).

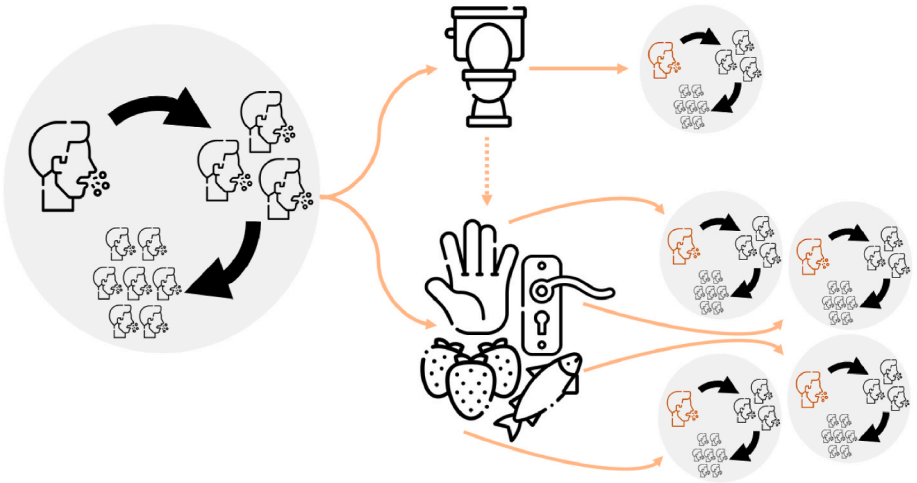

Fig. 2. Scenario PV2: Pandemic transmission of a respiratory virus via food. Person-to-person transmission of a pandemic respiratory virus (current situation, black) increases in the severity of spread after developing environmental stability (new transmission routes and infections in orange). Image icons designed by Freepik (www.freepik.com).

4.3. Strawberry and salmon as potential food chains for pandemic virus transmission

The economic effects of transmission of the two previously described pandemic foodborne viruses are studied in two food chains: the strawberry and the salmon chain, both fresh and frozen (Chapter 7). Strawberries and salmon can be consumed raw and are prone to virus contamination during several manual handling steps in the farm-to-fork continuum. Especially contamination early in the chain of foods that are subsequently traded frozen may result in virus spread that is dispersed in time and geography (Falkenhorst et al., 2005; Verhoef et al., 2011). Strawberries were chosen as soft fruits as they have been implicated in many international outbreaks (Bartsch et al., 2018; Müller et al., 2015; Petrović & D'Agostino, 2016) and have the highest trade volumes of consumed soft fruits (Food and Agriculture Organization of the United Nations, 2022a). Salmon was chosen as it can be consumed raw as well as cooked, requires multiple stages of food handling, and was one of the highly import-restriction affected chains in the COVID-19 pandemic (Ahmed & Azra, 2022). The cool climate and high humidity during slaughtering and processing may favor not only person-to-person transmission but also the spread and persistence of virus particles via the product (Chen et al., 2022).

Zoonotic or vector-borne transmission could also play a role in pandemic viral transmission via the food chain. Such transmission routes would have different impacts on the food chain and require different types of interventions than transmission routes via food ingestion and food or food packaging surface. In this study, these transmission routes are not further elaborated upon; nonetheless, it can be important for policymakers and other stakeholders to consider their eventual impact on our food system.

5. Hygiene codes for the scenarios and effectivity of sampling

In our scenarios, the introduction of a virus into the two food chains is the result of human fecal contamination or vomit and/or respiratory droplets. Depending on the potential introduction route of the virus, mitigation measures to prevent virus introduction would need to be selected.

5.1. Guidelines for the control of pandemic viruses in food

To give guidance on safe food preparation in case of a food-transmitted pandemic virus, existing guidelines for hygienic production of foodstuffs related to NoV and Coronaviruses (CoV) (Codex

Alimentarius Commission, 2012; European Commission, 2004; Food and Agriculture Organization of the United Nations, 2021; World Health Organization, 2022a; World Health Organization & Food and Agriculture Organization of the United Nations, 2020) were evaluated for their potential effectiveness to control the pandemic viruses in the two scenarios (Table 1). Table 1 shows that many measures target both virus types, although other measures might be only effective against one of the two. Since enveloped viruses, like those modeled in PV2, are usually less resistant to environmental conditions and treatments than non-enveloped viruses, like those modeled in PV1, measures to reduce PV1 from food and food processing areas are assumed to also reduce PV2. However, the effectiveness needs to be further evaluated specifically for a new pandemic virus as well as hurdles for compliance with the required measures. With respect to the effectiveness of virus inactivation, process steps need to be validated before implementation (Codex Alimentarius Commission, 2012) for the specific virus-matrix commodity. The possibility to do this may be limited to the availability and applicability of, e.g., viral infectivity assays or cultivable surrogate viruses (see Chapter 6). For this, and because monitoring of end-products cannot safeguard food (as argued in the next sections), prevention of contamination by the compliance of guidelines is important.

Studies on compliance with hand hygiene for the prevention of NoV and other food-borne pathogens indicate the importance of awareness, knowledge, sanitary facilities, time, and quality control (Boxman, 2013). The recent COVID-19 pandemic has shown that public awareness, education, and the severity of the disease can increase compliance with hand hygiene and willingness to wear personal protection equipment (PPE), like masks. Moreover, the recent pandemic also stressed the importance of the availability of raw materials to produce masks and laboratory testing materials (reagents, tips, etc.). In addition to personal hygiene measures and compliance with hygiene codes, innovations in the food sector and advanced traceability systems, if properly validated, could further increase the safety of food and handling thereof.

5.2. Monitoring and surveillance

Next to measures in food hygiene, in order to assess and mitigate the risks associated with a foodborne pandemic virus, monitoring and surveillance programs will need to be put into place. In this section, we explore the purpose and utility of such monitoring and surveillance strategies.

5.3. Sampling

Sampling can be performed for many reasons. There can be routine sampling, for example, to show compliance with microbiological criteria. Also, samples can be analyzed to identify hazards associated with product categories. In some situations (investigations, for special events), targeted sampling can be performed to answer specific questions. In case of a large outbreak or pandemic, increased sampling will also be performed. All these types of sampling will be discussed in the following sections.

5.4. Challenges of sampling strategies for highly infectious pathogens in food

Certain viruses are characterized by a very low infectious dose that is sufficient to infect 50% of a susceptible population (ID_{50}), making it unrealistic to prove safety by end-product testing. Taking the most frequent viral gastrointestinal agent as an example, for NoV, an ID_{50} of 18 particles is described (Teunis et al., 2020), meaning that one consumed particle already has a 2.8% probability of starting an infection. This implies testing is an ineffective tool to mitigate food safety, as will be explained below. In the following examples, it is assumed that the sub-sampling and analysis method is 100% effective. In practice, the

Table 1
Suggested hygiene measures for food safety with respect to Scenario 1: Pandemic transmission of a gastrointestinal non-enveloped virus via food (PV1) and Scenario 2: Pandemic transmission of an enveloped respiratory virus via food (PV2). Measures are modified from regulations for food safety with respect to NoV and SARS-CoV-2, based on EC[a], Codex[b], FAO[c,d] and WHO[c,e]. +: recommended; - not recommended; ± recommended under certain circumstances; ? needs further study.

Measures	Effective in reducing virus contamination		Remarks
	PV1	PV2	
General prevention			
Prevent fecal- and vomit-contamination of the environment and water	+	+	
Prevent airborne contamination	+	+	E.g., aerosols
Control of products/ ingredients	+	+	E.g., imported foods
GAP/GMP/HACCP [6)]	+	+	
Waste management	+	+	Including disposable equipment
Infection Prevention and Control			
Health status	+	+	Note: asymptomatic virus shedding (incl. shedding before or after symptoms) may occur
Vaccination	+	+	Limitation: Availability of vaccination
Easy availability of toilets	+	+	
Hand washing facilities in the vicinity of toilets	+	+	
Personal protective equipment	+	+	Gloves
Glove use procedure	+	+	Not a replacement for handwashing
Other personal protective equipment	?	+	Face masks, disposable overshoes, etc.
Hand sanitizing with ethanol-based gels	–	?	To be studied for effectiveness for PV2
Training on personal hygiene	+	+	Increase awareness of virus transmission
Physical distancing/barriers	?	+	Screens
Good respiratory hygiene	?	+	Coughing/sneezing in the elbow
Quarantine for ill personnel	+	+	PV1: return to work only after a period without gastrointestinal complaints
Strict regulations for non-employees	+	+	For entering the premises
Regular (extra) cleaning procedures	+	+	Consider the inclusion of disinfection
Cleaning and disinfection of the processing area			
Hygienic design of workspace	+	+	
Maintenance and cleaning	+	+	
Surface disinfection			
E.g., Chlorine, vaporized hydrogen peroxide, quaternary ammonium compounds	+/−	+/−	Dependent on disinfectant, treatment conditions and virus
Ultraviolet light radiation	+	+	For surfaces and water only
Alcohol-based sanitizers	–	+	Ethanol, propan-2-ol, propan-1-ol (>70%, sufficient contact time)
Processing steps to reduce the virus in food			
Cooling and freezing	–	–	
Heat treatment	+	+	Dependent on treatment conditions
Washing food products/ ingredients	+/−	+/−	Dependent on treatment conditions/food matrix – may

(continued on next page)

Table 1 (*continued*)

Measures	Effective in reducing virus contamination		Remarks
	PV1	PV2	
			reduce risk or cause additional cross-contamination
Adapt pH, water activity	?	?	Dependent on the virus (sub) type and conditions of treatment
Treatments such as high hydrostatic pressure, irradiation, cold plasma	+/−	?	Dependent on the virus (sub) type and conditions of treatment
Training			
Food business operators, food handlers	+	+	
Consumers: education, scientific outreach	+	+	Awareness of virus transmission routes is general and broader than food only

GAP/GMP/HACCP: Good Agricultural Practice/Good Manufacturing Practice/Hazard Analysis and Critical Control Point.

[a] European Commission (2004).

[b] Codex Alimentarius Commission (2012)

[c] World Health Organization and Food and Agriculture Organization of the United Nations (2020).

[d] Food and Agriculture Organization of the United Nations (2021)

[e] World Health Organization (2022a)

sensitivity and selectivity of methods are limited by, e.g., homogeneity of contamination in the batch, the virus extraction efficiency from the product, and the presence of inhibitory substances in the extract hampering the detection assay. Such effects largely reduce the efficiency of sampling plans (Zwietering and den Besten, 2016).

If in a batch of 1000 kg, there would be 1000 NoV particles, i.e., 1 particle per kg, and, with a 5 × 25 g = 125 g sample taken, this would give approximately 12.5% detection probability. With an estimated infection probability or $P_{inf}(1) = 0.028$ (based on an ID_{50} of 18 particles, i.e., $P_{inf}(1)$ can be estimated to be about 0.50/18), this one batch would result in 1000 × 0.028 = 28 cases. Not all infections result in illness; out of 28 infected persons, 19 developed acute symptoms of gastroenteritis (68%) (Teunis et al., 2008), and large uncertainty infection is assumed. When assuming a serving size of 50 g, this 1000 kg would be 20,000 servings, so the number of illnesses per serving would be 28/20000 = 0.0014 illnesses per serving. If a consumer has 50 servings per year (approximately one per week), this results in a yearly illness probability of 6.8% (i.e., 1-(1–0.0014)^50), and 67,000 people per million would then fall ill if this were the average contamination level.

The burden of such a foodborne disease can be estimated using disability-adjusted life years (DALYs), where 1 DALY represents one year of full health lost. In a report describing the disease burden of food-related pathogens in the Netherlands in 2019, it was estimated that 585,000 people in the Netherlands contracted a NoV infection (with 66 estimated to die and 1800 DALYs lost). Of these, 98,000 were calculated to contract NoV after the consumption of contaminated food, of which 7100 specifically after the consumption of produce (Lagerweij et al., 2020). With a Dutch population size of 17.4 million, this would mean 33,000 cases of NoV per million people, 5600 cases per million related to food, and 400 per million related to produce. Therefore, 67,000 people would fall ill per million due to a product category, strawberries in our example, that is a vehicle for this virus is too high of a risk. For lower levels of risk, more stringent plans would be required, but testing 5 × 25 g of a batch of 1000 kg is already very large and economically unrealistic. This example (assuming perfect methods and homogenously distributed virus particles) has been further worked out in Table 2 for varying batch sizes, the number of virus particles in the batch, the number of samples taken, weight per sample, and the number of servings of 50 g per person. Next to the detection probability, the estimated public health impact of various contamination scenarios is presented.

In Table 2, for most levels of contamination, the sampling plans have a very low probability of detection with 5 × 25 g samples. The level of contamination with a reasonable probability of rejection (71%, see the third row) detects batches with a level that would make everyone ill once per two years. Very low concentrations (10 particles) come to a realistic public health risk (69 illnesses per million people), and these have a very low probability of being detected or rejected. But higher concentrations, having a higher public health risk, still have a very low probability of being detected. In conclusion, although one can reduce the public health burden by safety testing, this shows that one cannot detect the majority of unwanted batches with a realistic sampling plan.

This calculation assumes high infectivity and that all virus particles are infective. Reduced environmental stability is expected for respiratory viruses (PV2) compared to gastro-intestinal viruses (PV1). Results also depend on the dose-response parameter selected that contains large uncertainty. Teunis et al. (2020) describe for NoV a strong variation of host susceptibility and virus pathogenicity, with a probability of illness from one virus particle between 0.0007 and 0.2 for a NoV genogroup I virus and between 0.015 and 0.035 for one virus particle for NoV genogroup II virus. In addition, Schmidt (2015) describes the probability of illness consuming 1 particle to be estimated from 0.00077 to 0.46 for various alternative fitted dose-response models.

Table 3
Effect of the proportion of infectious particles on detection probability and the public health impact with a sampling plan with 5 × 25 g samples for a batch of 10,000 kg containing 10,000 virus particles. A serving size of 50 g and 50 servings per year is assumed, and a homogeneous distribution of viruses.

Probability infectious particle	Probability positive for 1 sample	Probability positive from 5 samples	P_{inf}/serving	P_{inf} per year per person	Illnesses per year per million persons
1	0.0247	0.118	0.00139	0.0671	67,133
0.5	0.0247	0.118	0.000694	0.0341	34,138
0.1	0.0247	0.118	0.000139	0.00692	6921
0.05	0.0247	0.118	$6.94{\cdot}10^{-5}$	0.00347	3466
0.01	0.0247	0.118	$1.39{\cdot}10^{-5}$	0.000694	694
0.001	0.0247	0.118	$1.39{\cdot}10^{-6}$	$6.94{\cdot}10^{-5}$	69

Table 2
Effect of viral contamination levels on detection probability and public health with a sampling plan of 5 × 25 g samples. A serving size of 50 g and 50 servings per year is assumed, and a homogeneous distribution of viruses.

Batch size (kg)	Virus particles in the batch	Probability positive for 1 sample	Probability positive from 5 samples	Illnesses from such batch	P_{inf}/serving	P_{inf} per year per person	Illnesses per million persons
1000	100	0.0025	0.0124	2.8	0.000139	0.00692	6921
1000	1000	0.0247	0.118	28	0.00139	0.0671	67,133
1000	10,000	0.221	0.713	278	0.0139	0.503	503,073
10,000	10	$2.5{\cdot}10^{-5}$	0.000125	0.28	$1.39{\cdot}10^{-6}$	0.0000694	69
10,000	100	0.00025	0.00125	2.8	$1.39{\cdot}10^{-5}$	0.000694	694
10,000	1000	0.0025	0.0124	28	0.000139	0.00692	6921
10,000	10,000	0.0247	0.118	278	0.00139	0.0671	67,133

In case only a smaller proportion of the virus is infective (Table 3), and with a sampling plan of 5 × 25g, there is a very low probability of detecting batches that give an unacceptable health burden, except if we are really at the lower bound of Teunis et al. (2020) or Schmidt (2015). Even with only 1% infectious particles, the public health burden of a batch that has only a 12% probability of being detected can be considered not tolerable (namely, 694 illnesses would occur yearly per million people).

In Table 4, the calculated probability of obtaining a positive result for various sampling plans is depicted. This demonstrates that a very stringent sampling plan is needed (120 samples of 25 g) to detect even an unacceptable level of contamination equal to 67,000 illnesses per million people per year in the Netherlands, with more than 95% probability.

All these results are for the case of a homogenous, fully random distribution. In cases of clustering of virus particles, sampling will even be less performant.

It can therefore be concluded that microbial criteria and sampling to verify compliance cannot be used to prove safety. It can be useful, however: i) to detect extremely deviating batches; ii) for verification; iii) to obtain monitoring data; and iv) to give confidence in proper control by a long sequence of negative results over a longer time.

5.5. Monitoring

As shown above, sampling has a reasonable probability of detecting gross deviations, so sampling does not prove control, but an out-of-control situation can be detected. Long-term collection of sampling data from different companies can give an estimate of the potential overall risk of contamination and additionally can provide data for trend analysis to investigate if changes are occurring. Since positive detection is and should be very infrequent, only large, combined data sets will give sufficient information to draw some conclusions. This then provides information for national and international risk management or assessment and data for trends such as changes over time and geographical differences.

Li et al. (2022) reported the results of a very large monitoring study of SARS-CoV-2 contamination in frozen food-related samples, including swabs from food, packaging materials, environmental areas, and nasopharyngeal samples of employees. Out of 55.83 million samples, 1455 tested RT-PCR positive (0.0026%). Of 20.52 million food and food packaging materials, 1398 samples (0.0068%) were positive for RNA, of which 53.9% were from seafood and 37.9% from poultry or their packaging. The authors mention that current evidence shows that COVID-19 is neither a food safety issue nor a foodborne disease but that there is a risk for food handlers/operators, pointing towards the need to use effective PPE. This very large dataset illustrates several aspects mentioned above. If we would estimate the consumption of seafood in China to be about 70 million megatons (Godfrey, 2022) and assume that about half of the samples of food and food packaging material were from seafood (28 million samples), then despite the huge number of samples only 1 sample was taken from 2500 kg of product (about 25,000 servings of 100 g). If sampling were used for control, even this very large number of samples is by far insufficient to detect contaminated lots. However, this surveillance gives useful information for the prevalence of the virus RNA and can be used to analyze the risk of exposure of food handlers. It should be realized, however, that the prevalence might be uncertain due to potential false positive results (the positive rate is very low, and even a very low false positive rate might therefore have a large impact) and false negatives (due to methods, but also since not a whole serving is analyzed).

5.6. Targeted sampling, special events

In the case of specific situations (sewage leaks, floods, maintenance, etc.), it is relevant to additionally sample to gain some more confidence that the situation is not out of hand. Still, even with this additional sampling, no proof of control can be obtained, as shown above, since even with large sample sizes, too high levels of contamination can still go undetected.

5.7. Investigational sampling

In case of contaminated samples and food-borne outbreaks, additional sampling can help to trace down the source of the contamination and be used in root-cause analysis. In the case of several contaminated samples, relations between contamination sources can be investigated with genetic analysis of the detected viral RNA. In these cases, there is no one standard procedure, and an investigational plan should be made, also including epidemiological and ecological perspectives. Factors along the whole food chain could be relevant, like inactivation during processing, consumer handling, and various routes of contamination. This requires different types of sampling, analyses, and cooperation between different organizations, doing a thorough root-cause analysis.

6. Detection methods, virus culture and infectivity assays

6.1. Detection methods for foodborne viruses

Detection methods for viruses in food and environmental samples need to be very sensitive because of the low infectious doses. Furthermore, as discussed in Chapter 5, relevant volumes need to be processed to obtain a virus extract due to the distribution heterogeneity of viral particles. Sensitive detection is complicated as viruses, unlike bacteria, are dependent on host cells for replication. Food matrix-specific methods have been optimized to increase the recovery of various viruses from several food products and to reduce co-extraction of detection assay-inhibitory substances. As culture methods are not available in routine analyses, virus extracts are often subsequently extracted to obtain nucleic acids to be tested in molecular detection assays. Standardized and validated methods have been developed for the detection of NoV and hepatitis A virus RNA in soft fruits, leafy greens, bivalve mollusks, bottled water, and surfaces samples (International Organization for Standardization, 2019) and for quantification (International Organization for Standardization, 2017) using reverse transcriptase quantitative real-time PCR (RT-qPCR) (Lowther et al., 2019). Both ISO documents include quality controls and criteria for extraction and amplification efficiency to reduce the probability of false-negative results, though the absence of the virus in food can never be guaranteed. It is also widely accepted that the detection of viral RNA in a sample does

Table 4
Effect of the number of samples on detection probability and the public health impact for a batch of 10,000 kg containing 10,000 virus particles. A serving size of 50 g and 50 servings per year is assumed, and a homogeneous distribution of viruses.

Number of samples (n)	Weight per sample (g)	Probability positive for 1 sample	Probability positive from n samples	P_{inf}/ serving	P_{inf} per year per person	Illnesses per year per million persons
5	25	0.0247	0.118	0.00139	0.067	67,133
10	25	0.0247	0.221	0.00139	0.067	67,133
30	25	0.0247	0.528	0.00139	0.067	67,133
60	25	0.0247	0.777	0.00139	0.067	67,133
120	25	0.0247	0.950	0.00139	0.067	67,133

not directly demonstrate the presence of *infectious* viruses. This is because a small part of the genome is detected only, and RT-qPCR detection cannot provide information on the ability of the virus to multiply as an intact virus or the ability to cause infection (Manuel et al., 2018). Moreover, detected viral genomes may be derived from local virus aggregates, leading to an overestimation of the contamination level.

Interpretation of test results is not straightforward. When a food sample tests positive in an outbreak study, the epidemiological relation itself, or comparison of viral strains between patient and food, will add strength to the importance of the positive test result. However, what should be taken into consideration when a food sample tests positive in monitoring or surveillance? Besides the laboratory credibility, issues may include whether the sample is a raw or effectively processed food product, whether the product will be consumed raw or effectively processed, and what the expected public health risk is of the level of the detected contamination (Fig. 3). Processing raw products to reduce public health risks may lead to a loss of economic value (see Chapter 7). Therefore, there is a need for information on the infectivity of the detected viruses among regulators and food business operators.

6.2. Infectivity assays

Direct culture techniques using virus-replication supportive cell culture systems may provide information on the presence of infectious particles. The read-out system varies, e.g., detecting viral genomes in a cell lysate or culture supernatant, immunofluorescence staining of viral capsids in host cells, or cytopathic damage of host cells. For quantification of infective viruses in cell-culture systems, plaque counting can be used, or the Tissue Culture Infectious Dose 50 ($TCID_{50}$) can be determined. Plaque forming units (pfu) counting relies on cell lysis observed as clear zones in the cell-culture layer where monolayers of cells are covered with an agarose overlay after infection. $TCID_{50}$ is the concentration at which 50% of the cells are causing a cytopathic effect when the cells are inoculated with a dilution series of viral extract. In contrast to NoV, SARS-CoV-2 virus in clinical samples has been shown to replicate in Vero E6-based culture cell lines, and the $TCID_{50}$ could be determined, e.g., using a focus-forming assay in combination with a peroxidase-anti-peroxidase staining technique (Hiroi et al., 2021; Wurtz et al., 2021) or followed by genetic analysis such as genome sequencing (Zeng et al., 2022).

However, not all virus infections of cell cultures show a cytopathic effect. Moreover, in vitro culture systems are not available for routine analyses of many viruses such as NoV, despite efforts to accomplish such culture systems working with, e.g., B cells (Jones et al., 2015), Caco-2 cells (Pohl et al., 2022), human intestinal enteroids (Ettayebi et al., 2016; Hayashi et al., 2022), zebrafish larvae (Van Dycke et al., 2019), or animal models (Manuel et al., 2018). For this reason, culturable surrogate viruses, e.g., feline calicivirus, murine norovirus, or Tulane virus, have been used to predict the inactivation of NoV during processing or disinfection (Hirneisen & Kniel, 2013; United States Environmental Protection Agency, 2017). In order to circumvent the biosafety level classification of SARS-CoV-2 (Biosafety Level 3), studies have been performed with either a less pathogenic human CoV, for example, hCoV-229E, porcine transmissible gastroenteritis virus or murine hepatitis virus.

In general, culture techniques are time-consuming, the use of animal models is unwanted and requires specialized facilities, and both are

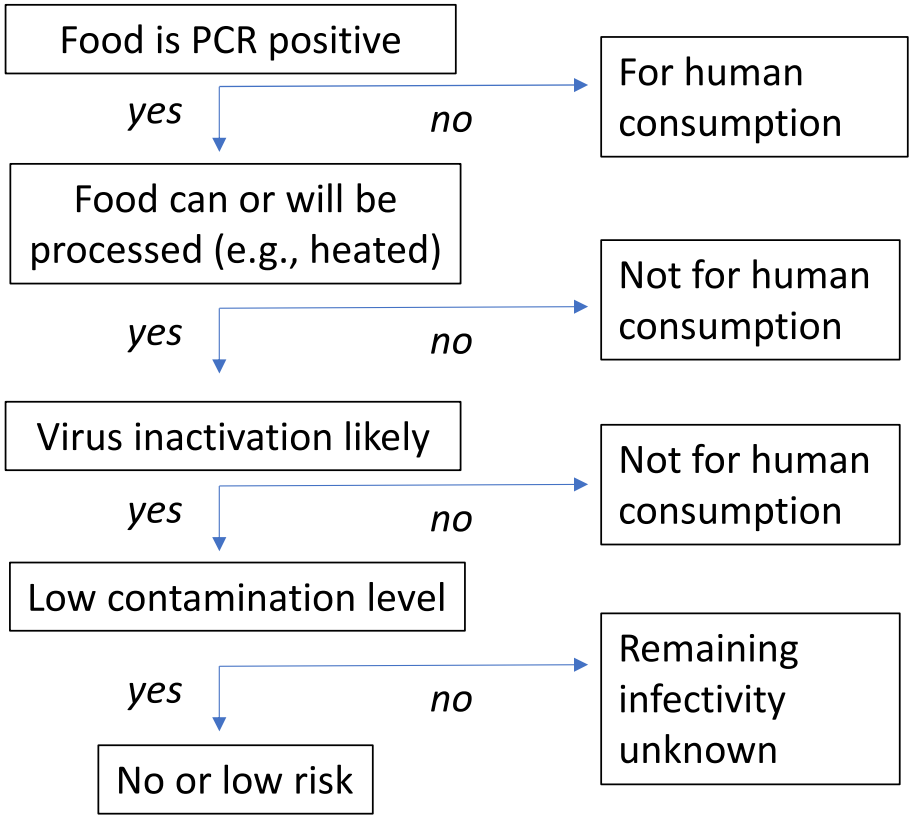

Fig. 3. *Assessment of the risk of consumption of viral RNA contaminated food.* When a food product, e.g., a sample of fresh or frozen strawberries, is tested positive for viral RNA, a decision tree can be used to estimate the public health risk. With PCR, it is unknown whether RNA is derived from infective viruses. Therefore, as a precautionary measure, the product should not be consumed without inactivation treatment. Strawberries can be processed, e.g., heated, to produce jam. With a low degree of contamination, it is very likely that no infectious viruses will remain. With high levels of contamination, the complete inactivation of infectious viruses also depends on the length of treatment and the internal temperature reached.

expensive, whereas results obtained with surrogate viruses must be interpreted with care as the surrogate may not behave similarly to the virus of interest (Bosch et al., 2018; Manuel et al., 2018). Moreover, testing food extracts for infectious viruses is challenging as the infectious virus particles need to be extracted from food without affecting the infectivity by the extraction method itself. In addition, the titer of the virus in the food extracts may be too low to observe virus replication in cell culture, or the food matrix itself, including the concomitant presence of bacteria and fungi, may negatively influence the outcome.

In order to circumvent all the above, several alternative techniques have been described to estimate the number of infective viruses, so-called proxy studies, which are listed in Table 5 and explained in Fig. 4. Some proxy studies are based on determining capsid integrity, as it is assumed that loss of integrity results in loss of cellular attachment or receptor binding and that the viral genome will be prone to degradation due to nucleases in the environment that can enter the capsid (Knight et al., 2013). The so-called viability PCR assay is based on viral capsid integrity as nucleic acid intercalating dyes, like propidium monoazide, can enter non-intact viruses only. Inside the virus capsid, and after exposure to strong visible light, the dyes bind covalently to the viral genome. This binding hampers the detectability of the genome by RT-qPCR. Viability assays have been used to examine the environmental stability of viruses or the effects of heat treatments or UV exposure on infectivity (Elizaquivel et al., 2014). Incomplete exclusion of RNA from inactivated viruses may lead to false-positive signals, and therefore, efforts need to be carried out to improve the efficacy of this approach or complement it with other strategies (Elizaquivel et al., 2014). Also, the degree of secondary structure present within the target RT-qPCR region, the level of interaction and protection by capsid proteins, the mechanical stability or plasticity of the viral capsid, or the level of viral aggregation within the sample may cause such a bias (Bosch et al., 2018).

Other principles measure intact viral genomes using sequencing or by detection of long target regions using PCR or use binding capacities to the intact cellular receptor (histo-blood group antigens) in porcine gastric mucin bound to magnetic beads or apply specific biosensors. Often, a combination of several principles is used as most assays provide partial insight into infectivity. The proxy assay of which the results mirror best the reduction of $TCID_{50}$ can depend on the inactivation process itself, e.g., heat treatment, ultraviolet light exposure, chlorine, etc.

Proxy assays have also been described for clinical samples. Some have described the application of NoV in environmental water, drinking water, or food samples. Proxy assays cannot always be incorporated into existing standard methods like ISO 15216, as the procedures already affect the infectivity of the viruses during extraction (Langlet et al., 2018; Razafimahefa et al., 2021). Therefore, they are not easily applied in monitoring. However, they have been used to collect data on inactivation conditions in laboratory settings, e.g., temperature, time, ultraviolet light exposure, and disinfectants, to predict the effect of strategies to reduce the risk of viruses. The collective data can be used as input to model the remaining virus infectivity during food processes, e.g., in a quantitative risk assessment. For reasons of experimental complexity, most infectivity studies have been performed on virus dilutions. It is, however, known that viruses in the context of tissue may differ in sensitivity to, e.g., heat compared to viruses in buffer only. Up to now, infectivity assays applied to viral extracts from food are hardly described but may be more common in the future. Recently, infectivity tests on GII.4 containing extracts from heat-treated clams were performed using enteroids (Hayashi et al., 2022).

Further research is, therefore, needed to investigate the application of these techniques for routine practice in food and environmental samples. Major challenges are the optimization of a virus extraction method suitable for all foods and environmental samples. The assays should be rapid, inexpensive, sustainable, and robust to detect infective viruses only and are applicable to whatever strain is in the sample (e.g., not all NoV strains replicate in enteroids). Another complication is that a proxy assay may provide partial information only, e.g., prove that the detected viral genome is derived from a virus that is able to bind and has a complete genome. When the next pandemic virus is transmitted between persons and via surfaces and food, the ultimate challenge will be to demonstrate that surfaces contain infective viruses and, moreover, to attribute illness to each transmission route (person-to-person, contagious surfaces, and consumption of food).

7. Economic effects

An outbreak of a pandemic virus that spreads via the foodborne route can be expected to have an enormous economic impact globally, potentially resulting in even higher costs than a pandemic in which food plays a negligible role. If the virus transmissibility, infectivity, and human health impact were like that of SARS-CoV-2, the economic impact of the SARS-CoV-2 outbreak could provide a preliminary indication of the economic impact of a non-foodborne pandemic. Laborde et al. (2022) estimated the short- and long-term impact due to the SARS-CoV-2 outbreak on the global gross domestic product (GDP) over the 2020–2030 period considering the policy and other measures taken

Table 5
Overview of recently published proxy assays to test for human norovirus (NoV) and SARS-CoV-2 (CoV) infectivity.

Assay	Principle	Types of samples tested	Available for NoV	Available for CoV	Example references
PMA combined with RT-qPCR	PMA (propidium monoazide) as an intercalating dye assay identifies capsid integrity combined with cycle threshold (Cq) values from the RT-qPCR	shellfish, sewage, water	+	+	Hong et al. (2021); Lee et al. (2016); Otaki and Kazama (2021); Randazzo et al. (2018); Sarmento et al. (2020)
LTR-PCR or WGS	Long target region or whole genome sequencing as an indication for intact virus	Water, clinical, and lab setting	+	+	Rodriguez et al. (2009); Wang et al. (2021)
Aptamers NoV	Mimics receptor-binding behavior and assesses capsid functionality	Clinical settings	+		Moore et al. (2016); Schilling-Loeffler et al. (2021)
Aptamers CoV	Tested on structural proteins (Nucleocapsid and spike glycoprotein) fluorescence measured with Enzyme-Linked Aptamer Binding Assay test (ELAA)	Clinical setting		+	Velázquez Roig and Rodríguez-Martínez (2022); Wandtke et al. (2022)
HBGA capture	HBGA (histo-blood group antigen) blockade correlates to the neutralization of live virus infections in vitro	Clinical setting	+		Sels et al. (2021)
PGM capture	Human intestinal enteroids HBGA binding and VLP-pig gastric mucin (PGM) binding assays	Virucidal hand rub testing	+		Ettayebi et al. (2022)
Electrochemical- and optical biosensors	Biorecognition elements: aptamers, synthetic specific peptides, polyclonal antibodies, SPR (Surface plasmon resonance)-based biosensor, bioluminescence-based biosensor)	Clinical setting	+	+	Azad et al. (2021); Cesewski and Johnson (2020); Jeewandara et al. (2022); Syed Nor et al. (2022)
Immuno (magnetic) capture	Antibodies against spike, nucleocapsid, or receptor-binding domain proteins.	Clinical setting, oysters	+	+	Gao et al. (2021); Ha et al. (2021); Schuster et al. (2022)

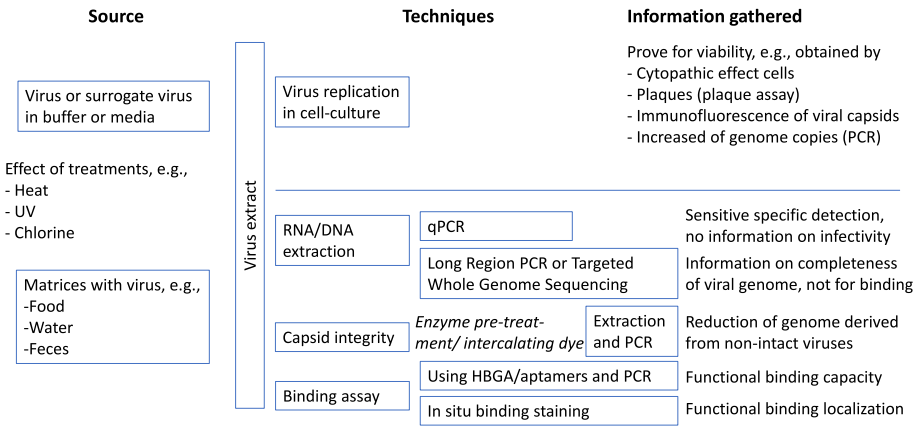

Fig. 4. *Techniques used to test for (effects of treatments on) virus infectivity*. Cells permissive to virus replication can be used to test the infectivity of (surrogate) viruses without or after exposure to inactivation treatments. For food/water/fecal samples, virus extraction from the matrix and subsequent concentration will be followed by exposure to the permissive cells. Proxy assays are independent of such cells but will only provide an estimate of infectivity, i.e., information on genome completeness, capsid integrity, or binding capacity.

to minimize the impact of the pandemic. They estimated a loss in global GDP per capita of 5.6% for 2020, 5.2% for 2021, 1.1% for 2025, and still, in 2030, a loss of 1.4%, thus showing the impact of the outbreak could extend to over a decade. Annual costs mount to several trillion USD, given that the global GDP is approximately 90 trillion USD (according to the World Bank, it was 87.65 trillion current USD in 2019). In line, McKibbin and Fernando (2021) estimated the global loss in GDP in 2020 alone to be between 0.3 and 9.1 trillion USD, with actual costs more likely closer to the upper value given that SARS-CoV-2 developed to be a global pandemic. Total costs over the years could amount to tens of trillion USD. Therefore, the costs associated with a pandemic virus are long-lasting and expensive.

When considering the effect of a pandemic virus on the agro-food sector, we saw, for instance, with SARS-CoV-2, rising prices due to disruptions in food supply chains and trade caused by measures to reduce the spread of the virus in society, such as lockdowns and social distancing. These disruptions included the closure of production facilities and ports, closure of restaurants and food services, a decline in passenger airline flights, restricted food trade policies, a lack of workers due to illness, and changing consumer preferences (Aday & Aday, 2020; Deconinck et al., 2020). This caused substantial problems in food security, especially for countries depending largely on food imports. Laborde et al. (2022) projected that, due to the pandemic, in 2021, globally, 72 million additional people have fallen into extreme poverty. This would increase to a projected 95 million in 2030. Similarly, they estimated 25 million additional undernourished people globally due to the pandemic in 2020, which would increase to a projected 37 million in 2030. Therefore, the costs associated with a pandemic virus can also extend beyond that of the agro-food sector, also affecting societal issues like food security. A food chain designed to maximize productivity and efficiency under standard conditions is likely relatively sensitive to market disruptions caused by a pandemic. Investments in a more resilient food chain can increase global food security during a pandemic (Galanakis, 2020), but strong evidence will be required to demonstrate that the benefits of policy interventions would outweigh the costs so that these interventions are also maintained without a pandemic (Hobbs, 2021). One example of a shift towards a more resilient market in developed countries could be seen during the COVID-19 'stay at home' policy, when e-groceries showed unprecedented growth (Dannenberg et al., 2020). However, when restrictions were removed, the market quickly returned to its state before lockdown policies with a corresponding level of food chain resilience. Efforts are needed to develop policy interventions to increase food availability and income in developing countries, which could improve food chain resilience and reduce the impact of a pandemic on food security.

With a foodborne pandemic virus, additional costs will arise to prevent foodborne transmission. Current foodborne viruses causing isolated outbreaks, smaller in size than a pandemic, already result in high costs. For example, global societal costs due to NoV were estimated at 60.3 billion USD per year, and global direct health system costs at 4.2 billion USD per year (Bartsch et al., 2016). Bartsch et al. (2020) estimated the annual costs of NoV in the USA at 10.6 billion USD, of which 95% concerned productivity losses and 5% direct medical costs, and sporadic cases generated over 90% and outbreaks less than 10%. They also showed that more than half the economic burden was concentrated in adults aged ≥45 years and over 90% of outbreak costs were due to person-to-person transmission. Johnston et al. (2007) also estimated the economic costs of a NoV outbreak in a tertiary care hospital in Baltimore (USA) during February–May 2004 at 650,000 USD, of which 420,000 USD lost revenue, 97,000 USD cleaning expenses, 89,000 USD due to sick leave and overtime, and 53,000 USD due to replacement medical and unit supplies. These estimates show that the costs of an outbreak can be high for even a single institution or company; the economic cost of a food-borne pandemic outbreak would be significantly higher.

Furthermore, in agri-food sectors, additional efforts will need to be made to prevent contamination of food products and packaging, monitor the virus, and inactivate the virus in food products and packaging. The costs can be expected to be higher than in the situation of SARS-CoV-2 because, in most countries, food products and packaging were not considered to be an important contributor to the spread. With a foodborne pandemic virus, current food safety control measures applied by companies will need to be adapted to the virus. Countries could also demand additional guarantees of the absence of the virus, such as implemented by China for SARS-CoV-2 (Rejeb et al., 2020) or to verify compliance with import requirements and control measures adopted by the exporting countries and regions (HKTDC Research, 2022). For example, Li et al. (2022) reported that from July 2020 to July 2021, over 55.83 million samples from frozen foods and their packaging were analyzed for the presence of SARS-CoV-2 RNAs by RT-qPCR. With costs of PCR reagents of approximately 8 USD per sample (in duplicate), total reagent costs alone are calculated at approximately 500 million USD. This excludes other costs, such as personnel and equipment. This example illustrates how the costs for additional efforts, as realized during the COVID-19 pandemic, could also increase the economic burden on the agro-food sector if a pandemic virus were to be food-borne.

Likewise, in the case where batches were found to be positive, recall of these batches is likely. Recalls can result in substantial direct and indirect costs and loss of corporate value (e.g., (Gunawan et al., 2022; Pozo & Schroeder, 2016; Velthuis et al., 2010)). It is expected that great

efforts will be put into developing methods to inactivate the virus in and on food products and packaging, especially in fresh and frozen products that lose value when heat treated. However, it is likely that such methods will not be directly available at the onset of the outbreak. Methods being currently developed for the inactivation of SARS-CoV-2 in food and on the packaging, for example, electron beam irradiation (Luo et al., 2023), could be potential candidates for this. Especially at the beginning of an outbreak, it can be expected that governments will carry at least part of the costs of such control measures. However, the longer a pandemic occurs, the more these costs will have to be carried by companies and, ultimately, consumers. Thus, diverse direct and indirect costs, effects on corporate value, as well as costs for method development and control can be expected for our pandemic scenarios, PV1 and PV2.

On top of this, the costs of efforts made in the agri-food sector will depend on the strictness of the implemented efforts. The strictness depends on the share of the food route in all infectivity routes and on the infectivity of the virus. A higher share of the food route and higher infectivity will likely result in companies in the agri-food sector being obligated to implement more and more strict efforts to prevent contamination and monitor the virus. This will result in higher costs. Therefore, it can be expected that more efforts will be mandatory from legislation and government policies rather than voluntary.

Finally, the costs of a foodborne pandemic virus also depend on the food types that could be contaminated with the virus. Are all food types involved, or only specific types? Consumers will likely avoid food that could be contaminated with the virus or have a higher probability of being contaminated and instead replace these with alternative foods that are not or are less associated with contamination. Demand, trade, and production of such contaminated products will probably collapse. With our selected scenarios, we gain some insight into the economic consequences if only specific food products, i.e., strawberries and salmon, were to be contaminated with the virus, be it scenario PV1 (Fig. 1) or PV2 (Fig. 2).

7.1. Strawberries

From 2015 to 2020, the global annual strawberry gross production value varied between 15.1 and 24.0 billion USD (Food and Agriculture Organization of the United Nations, 2022a). This encompasses strawberries for the fresh market and for processing, of which the larger part is for the fresh market. For example, Wahl et al. (2014) indicated that about 80% of the strawberries in the USA were for the fresh market and 20% for processing. A collapse of strawberry production would mainly impact China, the USA, the EU, and Mexico, where approximately 70% of global production occurs (Food and Agriculture Organization of the United Nations, 2022a). If a pandemic virus is transmitted via fresh and frozen strawberries, consumer demand for and trade in strawberries would likely collapse, given a limited shelf-life. Shifting from fresh to further processed strawberries would need to guarantee that the virus is inactivated and could only be done to the extent that processing capacity and demand are available, meaning that the rest of the product would probably have to be destroyed. Moreover, the part that can be shifted to processing would get a potentially substantially lower revenue price, depending on the local market circumstances and prices. For example, in the USA, Wahl et al. (2014) estimated a 60–80% difference in revenue price between 3.53 USD per kg of fresh strawberries and 0.66 to 1.43 USD per kg of processed strawberries, depending on the market situation.

Furthermore, a collapse in global trade would mainly concern countries in North America and in the EU because these exported approximately 88% of the global trade value of fresh and frozen strawberries of 3.3 billion USD in 2020 (Appendix Table A). The global trade value of fresh strawberries was estimated at 2.99 billion USD, almost two and a half times the 1.22 billion USD of frozen strawberries (Observatory of Economic Complexity, 2022a; 2022b). Given these numbers, it is likely that global costs would easily reach billions of USD if fresh and frozen strawberries were (the only) food products that could transmit a pandemic virus. If strawberries are associated with virus transmission, prices of processed strawberries most likely would collapse due to the large additional supply. If the outbreak starts after the production season, producers will likely shift to producing other crops, reducing the economic impact in the following years. Producers who want to keep producing strawberries must comply with strict biosecurity measures and be able to guarantee the absence of the virus. For example, the SARS-CoV-2 outbreak resulted in many labor-related challenges for strawberry producers because picking requires manual labor, such as checking workers for symptoms and monitor SARS CoV-2 outcomes, providing protective face covers, sanitizer, tissues, and handwashing stations for workers, and ensuring social distancing (Song et al., 2021). Such measures will need to be even more stringent if the virus can be transmitted via strawberries.

7.2. Salmon

From 2015 to 2020, the global annual salmon gross production value varied between 12.7 and 18.6 billion USD (Food and Agriculture Organization of the United Nations, 2022b). Furthermore, in 2020 global trade value was estimated at USD 15.0 billion for fresh salmon and USD 6.0 billion for frozen salmon (Appendix Table B). If a pandemic virus is transmitted via fresh or frozen salmon, global salmon processing will likely show a serious collapse because most producers of farmed salmon will likely be unable to switch to other fish, especially that related to aquaculture. For instance, the SARS-CoV-2 outbreak has severely disrupted Chile's salmon industry (Soto et al., 2021). Export markets were closed, quarantine measures made it difficult for workers and specialized personnel to tend farms (resulting in lowered growth rates, increased mortality due to diseases and parasites, starvation, and more fish escaping the ponds), and biosecurity measures for workers and government personnel complicated regular controls and monitoring of health and environmental issues. Also, social distancing resulted in processing plants being unable to work at full capacity (forcing a slowdown or stopping harvest from farm facilities), consequently leaving fish in the water beyond normal harvesting time. Thus, it will be of utmost importance for the salmon sector to implement measures to prevent contamination and to monitor the virus, which guarantees the absence of the virus, whether it is wild-caught or farmed.

A collapse of the salmon demand would mainly impact the two main producers and traders in Norway (50% of global production) and Chile (33%) (Food and Agriculture Organization of the United Nations, 2022b); although many other countries, like Poland and USA, import salmon. The Norwegian salmon industry was less affected by the SARS-CoV-2 outbreak, although differences between the type of products were observed (Straume et al., 2022). Many salmon producers would not be able to sell their fresh or frozen salmon anymore. Producers could shift selling processed salmon, for example, smoked, cured, or salted, if this processing would inactivate the virus. But this could only be done to the extent that demand and processing capacity are available; the rest would probably have to be destroyed or released in the wild. Therefore, it is easy to imagine that the global costs of an outbreak would easily reach billions of USD. Moreover, as workers contaminate the salmon in a cold chain environment that is similar for other frozen and fresh fish products, it is plausible that many additional fish chains will be affected, further increasing the economic impact.

7.3. Food

The results of the selected scenarios show that the economic impact can differ substantially between types of food products that can transmit the virus. Still, in both food chains, global costs are estimated to be in the billions of USD. It is important to note that only individual food products were examined. If a virus were to contaminate staple foods or food in

general, it would not be possible for consumers to avoid all the types of foods that could be contaminated with the virus and food security could be highly impacted. Food processing companies, retailers, and consumers probably will demand guarantees that the food products they purchase are free of the virus. Consumers will likely increase their preference for locally produced food, as was seen with SARS-CoV-2, due to the erosion of their trust in the global food system (Butu et al., 2020; Palau-Saumell et al., 2021; Rombach et al., 2022). Furthermore, consumers will have to implement control measures themselves to prevent infection, for example, sufficiently heating all products they consume. This could also involve a shift away from products eaten raw or without being heated at home, such as salads, fruits, or sushi.

International trade in food products could suffer severe consequences because clients and countries would likely demand a guarantee of the absence of the virus. Companies involved in the production and international trade of food products that could be contaminated with the virus will need to implement strict control measures. Which control measures will be sufficient is unclear, as are the consequential costs. If such a guarantee of absence cannot be given, trade in such products might decrease substantially. Next to potentially large economic consequences (according to the Food and Agriculture Organization of the United Nations (2022c)), global food and agricultural export value almost reached 1500 billion USD in 2020). Even if a small part of global trade is affected, this could also endanger global food security. Collectively, these calculations stipulate the major potential economic effects of a pandemic food-borne virus and emphasize the need for pandemic preparedness and further development of cost-effective control measures for viruses in food.

8. Conclusions and recommendations

In this study, the potential introduction and transmission of pandemic viruses via the food chain have been evaluated. Historical food (chain) related introductions of viruses into the human populations were featured and placed into the context of their high potential capacity for causing epidemics, suggesting the plausibility of a future viral pandemic that has a relation to the food chain. Viruses with high epidemic potential are described in relation to their stability and potential for foodborne transmission. Due to challenges in scientifically demonstrating the surface transmission of viral pathogens versus their airborne transmission, there is great incongruence in virus transmission models. Therefore, the food and fomite transmission component could be easily neglected or underestimated in a future pandemic. Access to improved methods to detect and model the transmission of pathogens would benefit our preparedness against the emergence and spread of future pandemic pathogens or provide confidence in our food system when it is shown that food and fomite transmission is not an issue. This message is important for food business operators and governments alike to understand the possible risk of pandemic viruses being introduced and transmitted via our food system and the potential knowledge gap surrounding surface and foodborne transmission.

If food is to become a vehicle for pandemic virus transmission, this would compromise food safety and food security and be of great impact on the economics of food systems. Various scenarios are possible depending on the nature of the virus, e.g., tissue specificity, tropism, and modes of transmission. To further discuss the global impact of a potential foodborne pandemic, two scenarios were hypothesized: (PV1) a pandemic caused by a highly stable and transmissible *gastrointestinal* virus via food with more severe illness and (PV2) a pandemic caused by a highly harmful and transmissible *respiratory* virus via food with improved environmental stability. These scenarios help disseminate the impact on the safety and availability of specific foods as well as related economic consequences and the size of economic damage, as this depends on the transmission route and other properties of the virus. In this context, the economic impact of a foodborne pandemic occurring in two food chains, the strawberry chain and the salmon chain, was calculated.

In scenarios PV1 and PV2, the introduction of the foodborne pandemic virus continually occurs via fecal or vomit and/or respiratory droplets. Guidelines will be required for the control of such a pandemic virus in the food chain. These will depend on the dissemination route of the virus. Specific hygiene measures required for the mitigation of a foodborne pandemic virus are suggested. Alongside hygiene measures, monitoring food for the presence or absence of viruses in specific chains will be necessary. Of note, it is not a realistic endeavor to ensure the safety of food by enforcement criteria due to the economically unfeasible amount of testing that is required in a pandemic scenario. Rather, food safety testing is recommended to detect deviating batches, for verification purposes, to obtain monitoring data, and to provide confidence of control and assess compliance to hygiene criteria. Due to challenges in culturing foodborne viruses, routine batch testing relies on the demonstration of the presence of short stretches of viral genomic material. It is widely accepted that this method does not demonstrate the presence of infectious viral particles. Research and development are needed to develop affordable and effective infectivity assays for high epidemic potential viruses so that (un)safety of the food chain can be properly demonstrated, and the economic impact can be reduced by acting early and well-informed. Application of such tools will further translate to a comprehensive understanding of surface and food consumption-mediated viral transmission routes that are currently lacking. This message is important for food business operators, policymakers, and scientists to understand the possible analytical needs, opportunities, and caveats for food safety testing.

In the unfortunate event that a viral foodborne pandemic crystallizes, economic costs will be great. The economic consequences were estimated for the strawberry chain, the salmon chain, and, more generally, for food. In cases where a specific product is affected, global costs will likely exceed billions of USD. If a virus were to contaminate staple foods or foods in general, consumers would be forced to implement control measures themselves or shift away from specific types of food, eventually potentially affecting global food security. This message illustrates the importance for food business operators and governments to appraise the potential economic costs of pandemic viruses being introduced and transmitted via our food system and to determine whether actions are needed.

In conclusion, if a pandemic virus associated with the food chain were to occur, our preparedness is currently lacking given our potentially limited knowledge of the transmission and introduction pathways, as well as access to methods to detect the viral presence and -infectivity and model the transmission of the pathogens. Likewise, cost-effective regulatory measures and control strategies would be required and would need to be tailored to the nature of the virus. Food safety testing using enforcement criteria would be economically unfeasible, meaning other control interventions beyond sampling like stricter hygiene, decontamination of the product, or possibly vaccination of food handlers may be required, yet would not be without their own risks and benefits. Overall, narrowing the knowledge gaps on introduction, transmission, economic impact, as well as improvement of analytical feasibility, is required to benefit our preparedness against the emergence and spread of future foodborne pandemic pathogens.

Author contributions

Conceptualization, all; methodology, all; formal analysis, all.; investigation, all.; data curation, all; writing—original draft preparation, all; writing—review and editing, all; visualization, all; supervision and project administration, J.L.B; and funding acquisition, all. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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