

Bacteriophages and dairy fermentations

Mariángeles Briggiler Marcó,¹ Sylvain Moineau² and Andrea Quiberoni^{1,*}

¹Instituto de Lactología Industrial (UNL—CONICET); Facultad de Ingeniería Química; Santa Fe, Argentina; ²Département de Biochimie, de Microbiologie et Bio-Informatiques; Faculté des Sciences et de Génie; Groupe de Recherche en Écologie Buccale; Faculté de Médecine Dentaire; Félix d'Hérelle Reference Center for Bacterial Viruses; Université Laval; Québec City, QC Canada

Keywords: bacteriophage, dairy industry, milk fermentation, lactic acid bacteria, phage control strategy

This review highlights the main strategies available to control phage infection during large-scale milk fermentation by lactic acid bacteria. The topics that are emphasized include the factors influencing bacterial activities, the sources of phage contamination, the methods available to detect and quantify phages, as well as practical solutions to limit phage dispersion through an adapted factory design, the control of air flow, the use of adequate sanitizers, the restricted use of recycled products, and the selection and growth of bacterial cultures.

Introduction

In a fermentative dairy process, lactic acid bacteria (LAB) growth and metabolic activities are needed to assure a high-quality final product. These microorganisms produce lactic acid via lactose fermentation, which leads to a rapid decrease in pH. Cheese and fermented milk manufacture depends, largely, on this factor, which is also crucial for ensuring control of pathogenic and spoilage microorganisms.¹

Bacteriophages or “phages” are viruses that infect bacteria. They are now believed to represent the most abundant biological entities with an estimated range of 10^{30} to 10^{32} total phage particles on earth, assuming that they outnumber bacteria about 10-fold.² These bacterial viruses are present in ecosystems where bacteria have been found, including man-made ecological niches such as food fermentation vats. The industry has been dealing with this biological phenomenon for many years now and has relied on a variety of practical approaches to control phages, which include adapted factory design, improved sanitation, adequate ventilation, process changes, improved starter medium, and culture rotation.^{3–5} Despite extensive efforts, however, phage infection of starter LAB cultures remains the most common cause of slow or incomplete fermentation in the dairy industry, and both researchers and industrial technologists are aware of regular, although unpublished, cases where phage infections actually cause product downgrading. Thus, the goal of this review is to make the reader aware of the relevance and implication of phage attacks in dairy fermentations, with special emphasis on the daily and practical aspects related to this problem in the dairy fermentative industry.

*Correspondence to: Andrea Quiberoni, Email: aquibe@fiq.unl.edu.ar
Submitted: 07/10/12; Revised: 08/07/12; Accepted: 08/16/12
<http://dx.doi.org/10.4161/bact.21868>

Performance of Starter Cultures in Dairy Fermentations

The growth of dairy starter cultures can be influenced by a number of factors including the raw milk quality, presence of antibiotics or sanitizers, bacterial interactions, and phages.^{6,7}

Raw milk composition. LAB have generally complex nutritional requirements. As a consequence, most LAB species can grow only in media where constituents like amino acids and vitamins are freely available. Even if milk provides this ideal growing environment, other components may act as inhibitors of LAB.⁸ The lactoperoxidase-thiocyanate-hydrogen peroxide system, as well as immunoglobulins naturally present in milk are among the known inhibitors affecting LAB activity. If hydrogen peroxide is present in milk as a metabolite of some microorganism, it combines with the lactoperoxidase to oxidize thiocyanate into products (sulfate, carbon dioxide, ammonia, and water) that will inhibit some LAB. Some bacteria, including LAB species, may also agglutinate in raw milk. Antibodies found in the globulin fraction of milk cause this effect. As a consequence bacteria can form clumps and sediment on the bottom of vats, causing slow or heterogeneous acid production. However, the inhibitory role of these compounds is mainly relevant when raw milk is used in cheese manufacture, since agglutinins and immunoglobulins are inactivated by heat treatments or homogenization process.

Leucocytes and lysozyme, also present in milk, have antimicrobial properties, the last being particularly resistant to thermal treatments. Normally, their levels are very low in milk, but increases due to mastitis and high somatic cell counts. An antibacterial activity is also frequently associated with lactoferrin, an iron-binding glycoprotein present in milk. Finally, antibiotics, which may enter milk due to the treatment of cows for bacterial infection of the udder, can also affect LAB growth and activity. Good quality raw milk should not contain antibiotic residues, but some reports point to these molecules as responsible for slow acidification during milk fermentation processes. The sensitivity of dairy starters to antibiotics will vary although in general, *Lactococcus* spp are much more resistant to penicillin, *Lactobacillus* spp to tetracycline and *Streptococcus thermophilus* to streptomycin.⁶

Bacterial interactions and phages. The acid production rate of some LAB strains might be increased in the presence of other microorganisms, such as *Micrococcus* spp, which either remove H_2O_2 or produce stimulating metabolites.⁹ In contrast low concentrations of free fatty acids may also be inhibitory to several

LAB strains. Low levels of these organic acids are present in fresh raw milk, with increasing concentration as consequence of the activity of psychrotrophic bacteria, such as *Pseudomonas* spp.¹⁰ Even if the ability of some dairy starters to produce bacteriocins is generally considered as a positive attribute for food safety reasons, this feature may be problematic when the antimicrobial spectrum includes LAB species.

Despite of the above, phage infection represents the most significant biological factor affecting industries that rely on bacterial growth and metabolic activities. Depending on the process stage in which the infection proceeds, consequences may vary from slow acid production to completely lost batches.¹¹ High pH values, high residual lactose concentration and insufficient lactic acid content are the result of phage attacks occurring during the early stages of the fermentation. In particular, the residual lactose might be the substrate for the growth and metabolic activity of spoilage bacteria that negatively affect the quality of the product. Besides the inadequate overall product quality, all these factors may constitute an optimum ecosystem for the growth of pathogens, with the serious consequences on the consumer health.

The recognized ubiquity of phages in dairies is the basis for studies aimed to control rather than to eradicate them.² For several reasons, cheese manufacture is the most affected process. Worldwide, large volumes of raw milk are daily fermented by LAB starters, with *Lactococcus lactis* being the most extensively used. Consequently, *Lactococcus lactis* phages are the best studied and documented over the world, followed by *S. thermophilus* phages.^{2,12} The number of reported *Lactobacillus* (*Lb.*) phages is notably lower, possibly due to the characteristics of processes involving this genus. However, several phages affecting fermentation processes driven by *Lb. helveticus*, *Lb. delbrueckii* subsp *bulgaricus* or *Lb. delbrueckii* subsp *lactis* were isolated and documented.^{13,14} Lastly, emerging data suggests an increasing occurrence of phages for specific probiotic LAB strains, especially *Lb. plantarum*, *Lb. acidophilus*, *Lb. casei* and *Lb. paracasei*, which are increasingly used in several fermented products.¹⁵

Phage Entry into Dairy Environments

Raw milk. It is now acknowledged that the most permanent source of new phages within dairy environments is through raw milk, with their concentration ranging between 10^1 and 10^4 phages per ml.^{4,16-23} Madera et al.⁴ reported that almost 10% of raw milk samples collected from different dairies in Spain contained infectious lactococcal phages. Several research groups have also reported that many dairy phages are able to survive milk pasteurization.^{18,22,24-26} Moreover, the concentration of phages is even higher if only thermized or raw milk are used to manufacture fermented milk products. Consequently, phages might enter the manufacturing process and accumulate rapidly during fermentation if phage-sensitive strains are used, reaching concentrations up to 10^9 phages per ml of cheese whey or per g of product,²⁷⁻³⁰ up to 10^8 plaque-forming units (PFU) per ml in brine,²² and up to 10^8 PFU per m³ in air.³¹⁻³³ Taken altogether, a great diversity of phages is naturally present in the raw milk ecosystem, thus the absence of phages in dairies is unreachable.

Factory environment. Although raw milk is the most logical source of phages in the industrial environment, several dispersion pathways may be occur in dairies. Aerosolization is currently recognized as an important route of dispersion.³⁴ Personnel movements or transport of equipment and/or raw materials might cause the dispersion of phage particles as an aerosol. The consequences of this aerosolization are even worse if dispersion is unrestricted between contaminated and uncontaminated zones. In addition, phages present in recycled by-products may also spread to the entire factory environment, since bioaerosols can remain in the air for long periods.^{34,35} Additional underestimated sources of phage contamination are the working surfaces in the dairy facilities. In a recent study,³³ a qPCR assay found evidence for the presence of genetic material from c2-like and 936-like lactococcal phages on a variety of surfaces, such as floors, walls, stairs, door handles, office tables, equipment, cleaning materials and pipes. Although it is unclear whether these phages were active or inactive at sampling, these data emphasize the relevance of correct sanitation measures as well as personal training to diminish the risks of phage infection.³³

Recycling of milk by-products. The dairy industry, particularly cheese manufacturing, recycles whey protein concentrates (WPC) to increase product yield and/or enhance attributes of the final product.³⁶⁻⁴⁰ However, such a process is risky due to the possible presence of phages in these ingredients.²⁹ Indeed, phage remained present in liquids (whey, WPC, etc) subjected to pasteurization and even stronger heat treatments, such as 95°C for several minutes.^{22,30,41} Moreover, salts, fat, saccharides, and whey proteins may protect phages from thermal damage, thus increasing the risk of this recycling practice. To compound the risk associated with WPC, whey is frequently concentrated (ultrafiltration or microparticulation), thereby increasing the phage levels due to the possible retention of virions by the membranes. A general recommendation to minimize problems associated with WPC should consider its addition only to a fermentation involving the use of significantly different starter cultures, such as mesophilic and thermophilic bacteria. It must also be noted that whey products derived from manufactures using natural undefined (unknown composition) starters should not be added to processes driven by defined (known composition) strain cultures. Natural starters often contain phages and those viruses represent a serious threat to the limited number of strains composing the defined starter cultures.¹

Prophages. Genome sequencing projects has confirmed that many LAB strains contains prophages.⁴² In fact, lysogeny is widely distributed among dairy lactococci and lactobacilli.⁴³⁻⁴⁹ A significant lower incidence of lysogeny was demonstrated in *S. thermophilus* species, as only a few strains (1 - 2%) were induced by mitomycin C, although others reported much higher frequencies (25%).⁵⁰ A recent study showed that 25 out of a collection of 30 probiotic strains of *Lactobacillus* contained inducible prophages.⁵¹ Putting these lysogenic LAB under certain environmental conditions such as heat, salt, antimicrobials, or starvation, may activate the induction prophages that will replicate, leading to the release of new virions. The latter can potentially infect sensitive strains if present in starter cultures.⁴⁴ Capra et al.⁵² isolated

two lytic phages for the strain *Lb. paracasei* A from pure cultures, indicating that both phages could most probably have evolved from a lysogenic state. Whenever possible, the presence of prophages as well as the risk of their spontaneous induction should be carefully investigated when selecting strains and designing cultures for specific industrial fermentation processes.²

It should be noted that detecting the presence of inducible prophages in lysogenic strains might involve several assays. Ideally, culture treatment with an inductor leading to cell lysis and the subsequent plaque formation is the first evidence of lysogeny. However, suitable indicator strains may be hard to find and thus, a negative result is not proof for the absence of inducible prophages. Observation under an electron microscope to visualize induced phages in a lysate may be an option.^{52,53} Even prophage remnants that have lost most of the phage genome, are not inert entities within bacterial chromosomes. Indeed, defective (and functional) prophages are source of genes to recombine with infecting virulent phages.⁵³⁻⁵⁸

Interestingly, lysogenic strains may not always result in detrimental consequences. Studies of controlled lysis of lysogenic bacteria have shown positive effects, such as a decrease in bitterness for some ripened cheeses, where the hydrolysis of casein-derived hydrophobic peptides is performed by intracellular bacterial peptidases released by phage lysis.⁵⁹ Prophages might also be responsible for the resistance of a lysogenic strain against infection by virulent phages. The protection is conferred by prophage genes, particularly superinfection exclusion genes, which might encode repressor molecules.⁶⁰

Classification of Dairy Bacteriophages: An Overview

According to the International Committee on Taxonomy of Viruses (ICTV), all known phages infecting LAB are tailed phages and members of the *Caudovirales* order. Tailed phages are, in turn, organized into three families: *Podoviridae*, *Myoviridae*, and *Siphoviridae*. *Podoviridae* members have short and noncontractile tails; myophages have tails with a contractile sheath and a central tube while siphophages have noncontractile tails.⁶¹

As previously stated, *Lactococcus* is the most extensively LAB used by the dairy industry and phages infecting this genus are the most studied. Lactococcal phages belong mainly to the *Siphoviridae* family, with a few being *Podoviridae*. Lactococcal phages are currently classified into 10 groups based on morphology and genomic sequence analyses. At least one genome from each lactococcal phage group is available.^{62,63} However, most lactococcal phages isolated from dairy fermentations belong to one of the three main groups: 936, c2, and P335.

A recent review of *Lactobacillus* phages reported 231 phages, 186 of them morphologically characterized.¹⁴ A total of 109 were siphophages, 76 were myophages, and only one belonged to the family *Podoviridae*. Before the availability of genomic sequences, the classification of *Lactobacillus* phages was based mainly on morphological observations and DNA homology, *Lb. delbrueckii* phages being the first to be classified in the 1980s.⁶⁴ Later, several completely sequenced *Lactobacillus* genome phages were assigned to a classification scheme based on the organization of

the structural gene module of the siphophages.⁶⁵ Further proposals for classification of *Lactobacillus* phages were based on the deduced proteomic trees, disregarding phage morphology, but the under-representation of *Lactobacillus* phages in these schemes might distort the impact of those phylogenetic trees.⁶⁶

All *S. thermophilus* phages reported to date are members of the *Siphoviridae* family, and can be assembled into two distinct groups according to their DNA packaging mechanism (*cos* or *pac*) and the number of major structural proteins.⁶⁷ Although a third group of *S. thermophilus* phages may have been uncovered recently.⁶⁸ A strict correlation exists between the presence of a particular set of major structural phage proteins and the mechanism of DNA packaging, demonstrating that *cos*-containing phages possess two major structural proteins in contrast to the *pac*-containing phages, which possess three major structural proteins. Moreover, a great diversity of streptococcal phages is often observed in cheese making, in contrast with a more homogeneous phage population in yogurt production facilities.¹² The diversity of phage populations in cheese making may be due to the rotation of multiple strains of *S. thermophilus* in starter cultures, as compared with yogurt starters.^{69,70} Genomic sequences are available for a few isolates of each group.¹²

Leuconostoc strains are present in some dairy mesophilic starters, most often mixed with lactococci.⁷ This combination is essential for most applications since *Leuconostoc* grows slowly in milk as compared with lactococci but its addition still provides specific dairy flavors. Very scarce information is available on the biology of *Leuconostoc* phages, possibly because few phage problems have been reported in the literature.^{30,71-74} On the other hand, *Leuconostoc* phages have been isolated during in coffee fermentation⁷⁵ and in sauerkraut fermentation brines.⁷⁶ Globally, most of these phages were assigned to the *Siphoviridae* and to the *Myoviridae* families. More recently, the first complete phage genome sequence from a *Leuconostoc* phage was reported.⁷⁷ Bioinformatic analysis revealed low similarity with other phage genomes, pointing out that this phage is a rather unique.

Detection and Quantification of Dairy Bacteriophages: A Brief Survey

Early phage detection in raw milk, ingredients or the dairy environment is designed to diminish and control phage attacks during the fermentation processes.⁷⁸ Two general types of phage detection methods are available: direct and indirect. Direct detection methods focus on detecting the presence of lytic phage particles or their components (DNA, proteins) in a sample. Standard microbiological methods, i.e., plaque assays, spot tests and activity tests, are usually applied to milk or fermented products (cheese whey and fermented milks). One of the advantages of this type of technique is discrimination between phage and non-phage inhibitors. Disadvantages include the requirement for a sensitive indicator strain and the relatively long time needed to obtain results. Therefore, molecular detection is a preferred method, especially because the assay time is much shorter. Several assays based on the polymerase chain reaction (PCR) have been designed and successfully applied to detect, or even classify,

Lactobacillus, *Lactococcus* and *Streptococcus* phages in different dairy matrixes, including cheese whey, cheese whey starters, and milk samples.⁷⁹ The detection limit of a classical one-step PCR method usually ranges from 10^4 - 10^7 PFU ml⁻¹, depending on the phage type and sample, but an additional phage concentration step will allow detection of as little as 10^3 PFU ml⁻¹. qPCR-based methods provide highly sensitive, rapid and real time monitoring of specific phages during the fermentation process. Rapid detection assays (no more than 30 min) of *Lb. delbrueckii* and *S. thermophilus* phages were recently reported, with 10^4 PFU ml⁻¹ and 10^5 PFU ml⁻¹ of milk as quantification limits, respectively.^{80,81} In a recent study, this methodology allowed the detection and enumeration of three groups (c2, 936 and P335) of lactococcal phages in goat's raw milk and whey with a low detection limit (10^2 UFP/ml) in about 2 h.⁸² However, it must be noted that these molecular methods do not discriminate between active and non-active phage particles since they detect phage DNA. Molecular detection techniques can also be too expensive and too specific for routine monitoring. Moreover, another major inconvenience common to all DNA-based detection methods is that they can only detect phages whose genome sequences are available. To overcome these limitations, PCR-based methods and classical microbiological assays might be used together to obtain more data about the phages contained in the sample (titers, host range, phage type).⁸³

Of the traditional indirect methods, the activity test is one of the most commonly implemented for routine analysis in dairy plants. The presence of phages in a sample is assessed as a decrease in acid production (compared with a phage-free control sample) by a starter or strain culture in sterile, steamed or pasteurized milk.⁸⁴ Important limitations must be considered for this assay, particularly for mixed strain starters, since phage-insensitive strains will continue to grow and acidify. Other detection methods, called indicator tests, are based on the reduction of an indicator compound (generally, methylene blue or bromochresol purple), due to culture acidification in presence and absence of sample filtrate.⁸⁵ If phages are present in the sample, a time delay or a failure in the color change is observed. As in the activity test, mixed cultures may mask the presence of phages, producing false-negative results.

Another indirect method proposed for monitoring the fermentation process involves flow cytometric analysis. Flow cytometry is based on the detection of cells with low mass that are found late in the lytic cycle. Detection of lactococcal phage infection by flow cytometry was recently reported with limits comparable to classical PCR methods (10^5 PFU/ml).⁸⁶

In this case, the authors observed that during phage infection the typical lactococcal chains are broken up while cells with low-density appeared and could be detected. Results of the study demonstrated that phage infection of *L. lactis* is fast and efficiently detected, in a real time and even at the first signs of phage attack. The detection was evidenced as early as 1 to 2% of the lactococcal cells were infected. On the other hand, the authors argued that large particles such as eukaryotic cells and fat globules should be removed in order to avoid the blocking of the flow cytometer.

Another indirect method is based on the detection of changes in the electrical impedance or conductance of the milk, due to a decrease in lactic acid production when a phage infection occurs.⁸⁷ In a recent study, García-Aljaro et al.⁸⁸ developed a rapid phage detection method based on the evaluation of impedance changes during infection of a host-biofilm established onto metal (platinum and gold) microelectrodes. The infection and subsequent host cell lysis was monitored by non-faradaic impedance spectroscopy in milk samples. In this case, an *Escherichia coli* phage and its host were chosen as models, but the methodology would be applicable to any dairy phage, as long as a suitable bacterial host can grow on the microelectrode surface. The simplicity of the assay and the possibility of miniaturization of the system are among the advantages.

Recently, a method combining epifluorescence microscopy and Atomic Force Microscopy (AFM) was reported to monitor the presence of phages.⁸⁹ Specifically, epifluorescence microscopy allows *Lb. helveticus* phage particles to be enumerated from phage-infected cultures, while AFM allow monitoring changes in phage and bacteria population during the infection process. Phage particles to be enumerated with epifluorescence microscopy require SYBR Green I staining, then the emitting green light results in a bright particle larger than the actual size of the virion, enabling it to be counted with a fluorescence microscope. As disadvantages, authors have highlighted that both virulent and non-virulent phage particles are counted by the epifluorescence microscopy. Considering these facts, the authors suggested a combined phage count approach, including plaque assay and epifluorescence, in order to determine the total viral abundance and host specificity in dairy samples.

As acknowledged the early detection of bacteriophage in milk, raw ingredients or by-products at any point during fermentation, is extremely helpful minimizing the detrimental consequences of phage attacks in dairy factories. Nevertheless, several characteristics must be taken into account when selecting a particular phage detection method, including the volume of milk transformed each day, the type of fermentation process, the starter culture used, the diversity of the phage population, and the risk or frequency of phage infections. Additional considerations include the requirement for rapid results, the quantification limit, and, finally, the cost of the assay.

Control Strategies in Dairy Plants

Since the presence of phages is unavoidable in dairy plant environments, phage control strategies are designed to control rather than eradicate them.²¹ Culture rotation programs, direct vat-inoculation of starters, careful handling and disposal of whey,⁹⁰ use of phage-inhibitory media, optimized sanitation, and use of starter cultures with increased phage resistance⁹¹ are some of the approaches applied to minimize phage spreading in dairy plants (Table 1).

Plant design, airflow, and equipments. The layout of a dairy factory is one of the critical factors for preventing phage infection. Contact between raw materials and waste (whey or water) should be avoided. Some examples include the physical separation

Table 1. Phage control strategies in dairies discussed in this review

Phage source	Control strategies	Application methodologies	Remarks
Factory environment	Factory and equipment design	Physical separation of plant areas	
		Use of specific manufacturing areas for distinct technologies	
		Use of filtered air under positive pressure	
		Control of bioaerosols	
	Process design	Optimization of the processing steps	
	Sanitation	Use of effective sanitizers and disinfectants	Efficiency depending on phage susceptibility, phage initial load and suspension media
		Physical treatments (UV light irradiation, photocatalysis)	
Raw milk	Refrigerated storage of raw ingredients		
	Sanitation	Thermal treatments of raw materials and ingredients	Efficiency depending on phage susceptibility, phage initial load and suspension media
		High pressure technologies	Under laboratory tests only
	Direct vat-inoculation starters		Available for all types of processes
	Use of starter cultures with increased phage resistance	Bacteriophage-insensitive mutants	Simple methodology, without regulatory restrictions, valid to many LAB species
		Bacteriophage-resistant derivatives	Strains containing natural phage resistance mechanisms
		Genetically Modified Organisms	Available only in a few countries
Culture rotation programs		Suitability for many types of processes excluding probiotic products. Increased phage diversity	
Water as ingredient	Use of microbiologically safe water		
Processed or recycled ingredients (whey, i.e.)	Adequate whey handling	Avoiding bioaerosol generation (closed drains, i.e.)	Efficiency depending on phage susceptibility, phage initial load and suspension media
		Sanitation before recycling (thermal treatments)	
		Adequate disposal	
		Limiting the recycling of the final waste within the plant	
Lysogenic strains	Assessment of their absence when designing/selecting defined starter cultures		

of the milk reception from other plant areas, as phage-containing aerosols can be generated during tanker emptying and raw milk spillage. The starter preparation room should be sealed off from the manufacturing area and maintained under a positive pressure of filtered air. Another concern involves the whey tanks and separators, which should be placed in a separate area situated as far as possible from the starter room and the cheese manufacturing vats.

Avoiding the generation of bioaerosols as well as limiting the air microbial count by using spray systems with appropriate disinfectants should help in controlling infections.²¹ Additionally,

the air used for positive pressure applications must be filtered to remove dust particles, which may bind phages, and the air inlet for the filters should be located as far as possible from the milk silos and whey tanks. Finally, the efficiency of the filters should be checked regularly.^{21,92}

Stainless steel with a high grade of polish is the ideal material for all the equipment used in the fermentation processes, as it should be subjected to an efficient cleaning and sanitizing before and after use. The fermentation tanks must be closed, sterilized by heat or sanitizers, with positive pressure filtered air in

the headspace; the tanks should be monitored periodically for cracks.⁹²

Factory sanitation. A strict system for cleaning and disinfection of equipment and utensils used during processing are mandatory for maintaining phage levels as low as possible, and minimizing the risk of phage infection and dissemination within the dairy. No compromise should be made here. Several factors should be considered when selecting a sanitizer, including a fast antimicrobial activity, ease of application, low cost, lack of negative impact on the final product, and degradation into harmless final compounds. The effectiveness on phage inactivation is a criterion taken into consideration only recently, which is reflected by an increasing number of studies on their viral effectiveness.

Peracetic acid-containing products are often the most effective, assuring fast and efficient inactivation of phage particles. Sodium hypochlorite, ethanol and isopropanol, typically used for cleaning laboratory surfaces and utensils, are notably less effective in the inactivation of viruses.⁹³ Recently, the effectiveness of several classic biocides used by the dairy industry was evaluated on phages infecting *Lb. delbrueckii*,⁹⁴ *Lb. casei* and *Lb. paracasei*.⁹⁵ Biocides at extreme pH, such as alkaline chloride foam or ethoxylated nonylphenol with phosphoric acid (pH values > 12 and < 2, respectively), were exceptionally efficient, although pH level is not the only factor to take into consideration when choosing a biocide.⁸³ While quaternary ammonium chloride was efficient,⁹⁴ p-toluensulfonchloroamide showed no reduction in phage numbers.⁹⁵

As phage particles can remain in the air for long period of time, bioaerosols are one of the most important dispersion routes of virions. Very few studies have addressed this issue. For example, little data are available on the viral efficiency of fumigation/fogging systems, ozone treatment, and UV light irradiation in industrial facilities. The photocatalytic properties of TiO₂ have been investigated, but mainly for the photochemical pollutant oxidation. Several advantages of photocatalysis, such as low cost, high abundance and safety of TiO₂, the absence of residues, treatment of pollutant mixtures, broad range and ease of operation, suggest this methodology as an alternative to the traditional chemical disinfection. Semiconductor TiO₂ generates highly oxidizing species (O₂⁻ and ·OH) when photoexcited by UV radiation, thus catalyzing various chemical reactions, including the decomposition of organic compounds. Photocatalysis application has been mostly intended to destroy fungi, bacteria and spores in the air,⁹⁶⁻¹⁰⁵ but its efficiency for inactivating viruses in bioaerosols has been explored only recently. Kakita et al.⁹⁶ and Kashige et al.⁹⁷ have reported the inactivation of LAB phage PL-1 (*Lb. casei*) liquid suspensions using a ceramic preparation coated with a mixture of oxides (TiO₂ and AgO) and black-light (BL) (300 - 400 nm). Reduction of 6 logs were reported for *Lb. delbrueckii* and *Lb. plantarum* phages after photocatalysis exposure for less than an hour while two hours was needed for *Lb. casei* and *L. lactis* phages.^{23,35}

Ingredients treatment and recycling of products. From the time of collection, immediate refrigerated storage of milk is required to diminish the risk of microbial propagation including bacterial viruses. Depending on the type of product to be

manufactured, the milk undergoes different heat treatments to reduce microbial load (pathogens and spoilage). These heat treatments also indirectly reduce viral titers.⁹² However, a remarkably high thermal resistance has been reported for some phages infecting *L. lactis*, *S. thermophilus*, *Lb. casei* and *Lb. paracasei*, even up to 5 min at 95°C.^{15,22} High levels of thermo-resistant phages (10⁹ PFU / ml) have also been found in whey, brine and cream. Thus, the recycling of these by-products should be avoided since the return of even small quantities of phages can lead to constant propagation. Consequently, adequate heat treatment of by-products, prior to recycling, is recommended in order to reduce the problems associated with recontamination.^{30,106} It is recognized, however, that the physical properties and function of whey proteins can be severely affected by treatments to minimize phage load in by-products.⁸³

Inactivation of dairy phages using technologies involving high pressure has been explored.¹⁰⁷⁻¹¹⁰ The most studied and applied pressure-based processes are high hydrostatic pressure (HHP) and high pressure homogenization (HPH). Moroni et al.¹⁰⁷ demonstrated a significant difference in sensitivity to HPH between the two morphological types of lactococcal phages: prolate-headed (c2-like) were less stable than isometric-headed (936- P335-like). Others observed reduction of 2 to 6 logs for phages of *Lb. paracasei*, *Lb. casei*, *Lb. delbrueckii*, *Lb. plantarum*, *Lb. helveticus*, *S. thermophilus* and *L. lactis*, after 5 passes at 100 MPa in reconstituted skim milk.^{95,109} The phage inactivation rate was proportional to both applied pressure and number of passes. The influence of suspension media (milk, whey permeate, buffer) was variable, with the results dependent on the phage tested and authors.^{107,109}

Similarly, HHP has been proposed as an alternative to the thermal treatments applied in food preservation.¹¹¹ Little data are available on HHP, although inactivation of some dairy phages has been reported and seems variable from one phage to another. Specifically, *L. lactis* phages P001 (c2-like) and P008 (936-like), suspended in enriched M17-broth, were treated at up to 600 MPa.¹¹² The isometric phage P008 was considerably more resistant, with a 5-log reduction in concentration after treatment for 2 h at 600 MPa, whereas the same titer reduction was obtained for prolate phage P001 during the pressure-build-up time. Only an exhaustive analysis of costs, involving the estimated yield and the desired product characteristics, would help dairies to select alternative treatments to be applied to raw materials and the dairy environment in order to diminish the risk of phage infections.

Phage inhibitory media. Culture media might be designed to contain components that inhibit or delay phage propagation. For example, one strategy use culture media containing chelating agents, such as phosphates or citrates, capable of binding divalent cations, which are often needed to successfully complete the phage lytic cycle.⁷⁸ The use of sodium tripolyphosphate-high solubility (TAS) at low concentrations (0.3 to 0.5%) in milk was effective at inhibiting the lytic cycle of LAB phages.^{5,113} However, some bacterial strains showed a delayed growth and acidification profile, possibly due to the buffer ability of the added phosphates. Another technology used purified phage peptides as an

additive to protect a lactococcal culture, though phages were not inactivated.¹¹⁴ The peptides were able to extend the growth of *Lactococcus* culture in phage-containing L-M17 medium and milk. The culture was even protected from phage infection through renneting and ripening stages when the starter culture bulk was prepared in a medium containing the phage peptides.

Starter cultures. The use of natural starters composed of an undefined mixture of different strains and/or species is still the key for the production of many traditional cheeses in various countries.¹¹⁵ These artisanal starters are considered to be highly tolerant to phage infection because they are grown in the presence of phages, which lead to the dominance of resistant or tolerant strains. However, the limited reproducibility of their technological performance has led to the replacement of these traditional starters by direct multi strain cultures (DSC) in the production of many industrial large-scale cheese varieties. The strain and/or species in DSC are perfectly defined and their technological performance is highly reproducible. However, as a consequence of the limited number of strains used, a phage infection may cause the disruption of lactic acid fermentations. The use of concentrated DSC, added directly to the vat (Direct Vat Inoculation cultures - DVI) constitutes an alternative without need for on-site starter propagation, therefore, diminishing the risk of infection by phages from the cheese factory environment. Moreover, rotation of these cultures is probably the main basis for an efficient phage control program: avoiding recontamination by the same phage and build-up of high phage levels in a cheese plant. Although this strategy is not suitable for all dairy manufacturing processes, it provides a relatively simple way to minimize fermentation failures due to phages.⁸³ As a consequence, recent efforts have been made to search for potential new starter bacteria from the pool of wild strains recoverable from raw milk, undefined cultures, or traditional dairy fermented products. Hence, LAB strains with dairy-grade (e.g., antibiotic susceptibility) or pro-technological (e.g., broad phage resistance, high acidification activity, lack off-flavor development) traits are highly valued.¹

The extended co-survival of LAB and phages in the same environment has prompted the strains to acquire a variety of native phage defense systems.¹¹⁶ These mechanisms include inhibition of phage adsorption, blocking of DNA injection, restriction/modification systems, CRISPR-Cas systems and abortive infection (for a list of reviews on this subject see Garneau and Moineau⁸³). In lactococci, these mechanisms may be encoded by chromosomal or plasmid genes. Interestingly, natural gene transfer by conjugation of plasmid DNA is a common feature of lactococci. So, the conjugation of native phage resistant plasmids has been a profitable strategy for genetically improving dairy LAB for over 20 y, yielding multiple dairy starter cultures that have been in commercial use for many years, many of them under worldwide patent.^{3,117} However, although the conjugal transfer of phage resistance plasmids represents one of the most convenient, simple, and “natural” strategies to improve starter strains, the isolation of bacteriophage-insensitive mutants (BIMs) is an alternative for bacteria without conjugative plasmids. Several studies have described the isolation of spontaneous phage resistant

variants from sensitive strains of lactococci,^{118,119} *S. thermophilus*,¹²⁰⁻¹²³ *Lb. helveticus*,¹²⁴⁻¹²⁷ *Lb. delbrueckii*,¹²⁸ *Lb. casei* and *Lb. paracasei*¹²⁹ strains. Though there are some disadvantages to this methodology (e.g., a high frequency of phenotype reversion and physiological bacterial modifications), the isolation of BIMs has gained recent popularity because it is simple and involves no genetic manipulation, thus there are no regulatory restrictions to applications in industrial environments. The mechanism involved in BIM generation has been attributed to mutations in the phage receptors,^{120,130,131} even though recent studies have demonstrated that CRISPR-Cas systems^{121,123} or abortive infection systems¹³² play a role in the development of BIMs.

Over the past 25 y, the construction of genetically engineered strains has been intensively studied as an alternative to the development or use of transconjugants or phage-resistant mutants. Several genetic tools, based on the characterization and exploitation of the LAB native phage defense mechanisms as well as some phage genetic elements,^{3,133} have been designed. These antiphage approaches include origin-derived phage-encoded resistance, antisense RNA technology, phage triggered suicide systems, overproduction of phage proteins, DARPs, and neutralizing antibody fragments.^{11,83} Nevertheless, despite intensive research and economic support, dairy and starter culture industries have not benefited as expected mainly due to modest progress in the development of legislation regarding Genetically Modified Organisms.

Controlling phage infections of probiotic bacteria is starting to be documented and may become a new challenge. The manufacture of certain types of probiotic products involves propagation of the strains as a starter¹³⁴⁻¹³⁷ making them particularly vulnerable to phages.¹³⁷ Also, *Lactobacillus* strains have long been known to harbor prophages, yielding the possibility of spontaneous prophage induction during use, or of prophage DNA involvement in the generation of new virulent phages.⁵¹⁻⁵³ For probiotic phages, control strategies are limited as strain rotation is likely not possible and specific health claims may not be directly applicable if a phage-resistant derivative is generated.

Concluding Remarks

The risk of phage infection in processes relying on bacterial growth is here to stay. Despite significant progress made over the past decades to reduce the overall problem associated with phage contaminations, improvements are still needed. Ideally, fast and online tools that would detect amplifying phages would be a welcomed addition for most industries relying on bacterial growth. New technologies to remove phages from raw materials and by-products as well as air and equipments are still needed. Finally, a better understanding of phage-host interactions is an ongoing venture to appropriately select or develop bacterial strains for long-term industrial use in phage-contaminated environments.

Acknowledgments

We thank B.D. Conway for editorial assistance. S.M. acknowledges funding from the Natural Sciences and Engineering

Research Council (NSERC) of Canada. S.M. holds a Tier 1 Canada Research Chair in Bacteriophages. A.Q. acknowledges funding from the Agencia Nacional de Promoción Científica

y Tecnológica (ANPCyT, Project PICT 2010, 0138) and the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, Project PIP 2009 N°01206) of Argentina.

References

1. Carminati D, Giraffa G, Quiberoni A, Binetti A, Suárez V, Reinheimer J. Advances and trends in starter cultures for dairy fermentations. In: Mozzi F, Raya R, Vignolo G, eds. Biotechnology of lactic acid bacteria: Novel applications. Iowa, USA: Wiley-Blackwell 2010; 177-192.
2. Emond E, Moineau S. Bacteriophages and food fermentations. In: McGrath S, van Sinderen D, eds. Bacteriophage: Genetics and Molecular Biology. Horizon Scientific Press/Caister Academic Press 2007; 93-124.
3. Moineau S. Applications of phage resistance in lactic acid bacteria. Antonie Van Leeuwenhoek 1999; 76:377-82; PMID:10532393; <http://dx.doi.org/10.1023/A:1002045701064>.
4. Madera C, Monjardín C, Suárez JE. Milk contamination and resistance to processing conditions determine the fate of *Lactococcus lactis* bacteriophages in dairies. Appl Environ Microbiol 2004; 70:7365-71; PMID:15574937; <http://dx.doi.org/10.1128/AEM.70.12.7365-7371.2004>.
5. Suárez VB, Capra ML, Rivera M, Reinheimer JA. Inactivation of calcium-dependent lactic acid bacteria phages by phosphates. J Food Prot 2007; 70:1518-22; PMID:17612087.
6. Surono S, Hosono A. Starter cultures. In: Fuquay J, Fox P, McSweeney P, eds. Encyclopedia of dairy science 2^o Edition (Volume 2). Academic Press, Elsevier Science, USA 2011; 477-482.
7. Suárez V, Reinheimer J, Quiberoni A. Bacteriophages in dairy plants. In: Quiberoni A, Reinheimer J, eds. Bacteriophages in dairy processing, Nova Science Publishers, 2012; pp. 53-78.
8. Mäyrä-Mäkinen A, Bigret M. Industrial use and production of lactic acid bacteria. In: Salminen S, von Wright A, Ouwehand A, eds. Lactic acid bacteria: microbiological and functional aspects, 3^o Edition, New York, Marcel Dekker, Inc. 2004; 175-198.
9. Nath KR, Wagner BJ. Stimulation of lactic acid bacteria by a *micrococcus* isolate: evidence for multiple effects. Appl Microbiol 1973; 26:49-55; PMID:4199337.
10. Ringø E, Bendiksen HR, Gausen SJ, Sundsfjord A, Olsen RE. The effect of dietary fatty acids on lactic acid bacteria associated with the epithelial mucosa and from faecalia of Arctic charr, *Salvelinus alpinus* (L.). J Appl Microbiol 1998; 85:855-64; PMID:9830121; <http://dx.doi.org/10.1046/j.1365-2672.1998.00595.x>.
11. Quiberoni A, Suárez VB, Binetti AG, Reinheimer JA. Bacteriophage. In: Fuquay J, Fox P, McSweeney P, eds. Encyclopedia of dairy science 2^o Edition (Volume 1), Academic Press, Elsevier Science, USA 2011; 430-438.
12. Quiberoni A, Moineau S, Rousseau GM, Reinheimer J, Ackermann H-W. *Streptococcus thermophilus* bacteriophages. [Review]. Int Dairy J 2010; 20:657-64; <http://dx.doi.org/10.1016/j.idairyj.2010.03.012>.
13. Brüssow H, Suarez JE. *Lactobacillus* phages. In: Calendar R, Abedon ST, eds. The bacteriophages, 2^o Edition, Oxford University Press, New York 2006.
14. Villion M, Moineau S. Bacteriophages of *lactobacillus*. Front Biosci 2009; 14:1661-83; PMID:19273154; <http://dx.doi.org/10.2741/3332>.
15. Capra ML, Binetti AG, Mercanti DJ, Quiberoni A, Reinheimer JA. Diversity among *Lactobacillus paracasei* phages isolated from a probiotic dairy product plant. J Appl Microbiol 2009a; 107:1350-7; PMID:19486389; <http://dx.doi.org/10.1111/j.1365-2672.2009.04313.x>.
16. Quiberoni A, Suárez VB, Reinheimer JA. Inactivation of *Lactobacillus helveticus* bacteriophages by thermal and chemical treatments. J Food Prot 1999; 62:894-8; PMID:10456743.
17. Binetti AG, Reinheimer JA. Thermal and chemical inactivation of indigenous *Streptococcus thermophilus* bacteriophages isolated from Argentinian dairy plants. J Food Prot 2000; 63:509-15; PMID:10772217.
18. Suárez VB, Reinheimer JA. Effectiveness of thermal treatments and biocides in the inactivation of Argentinian *Lactococcus lactis* phages. J Food Prot 2002; 65:1756-9; PMID:12430698.
19. Quiberoni A, Guglielmotti DM, Reinheimer JA. Inactivation of *Lactobacillus delbrueckii* bacteriophages by heat and biocides. Int J Food Microbiol 2003; 84:51-62; PMID:12781954; [http://dx.doi.org/10.1016/S0168-1605\(02\)00394-X](http://dx.doi.org/10.1016/S0168-1605(02)00394-X).
20. Capra ML, Quiberoni A, Reinheimer JA. Thermal and chemical resistance of *Lactobacillus casei* and *Lactobacillus paracasei* bacteriophages. Lett Appl Microbiol 2004; 38:499-504; PMID:15130146; <http://dx.doi.org/10.1111/j.1472-765X.2004.01525.x>.
21. Moineau S, Lévesque C. Control of bacteriophages in industrial fermentations. In: Kutter E, Sulakvelidze A, eds. Bacteriophages: biology and applications. CRC Press, Boca Raton, FL 2005; 285-296.
22. Atamer Z, Dietrich J, Müller-Merbach M, Neve H, Heller KJ, Hinrichs J. Screening for and characterization of *Lactococcus lactis* bacteriophages with high thermal resistance. Int Dairy J 2009; 19:228-35; <http://dx.doi.org/10.1016/j.idairyj.2008.10.012>.
23. Briggiler Marcó M, De Antoni GL, Reinheimer JA, Quiberoni A. Thermal, chemical, and photocatalytic inactivation of *Lactobacillus plantarum* bacteriophages. J Food Prot 2009; 72:1012-9; PMID:19517728.
24. Chopin MC. Resistance of 17 mesophilic lactic *Streptococcus* bacteriophages to pasteurization and spray-drying. J Dairy Res 1980; 47:131-9; PMID:6768773; <http://dx.doi.org/10.1017/S0022029900020963>.
25. Müller-Merbach M, Neve H, Hinrichs J. Kinetics of the thermal inactivation of the *Lactococcus lactis* bacteriophage P008. J Dairy Res 2005a; 72:281-6; PMID:16174358; <http://dx.doi.org/10.1017/S0022029905000725>.
26. Abedon TS. Bacteriophage ecology: Population growth, evolution, and impact of bacterial viruses. Cambridge, UK: Cambridge University Press 2008; 302-332.
27. McIntyre K, Heap HA, Davey GP, Limsowtin KY. The distribution of lactococcal bacteriophage in the environment of a cheese manufacturing plant. Int Dairy J 1991; 1:183-97; [http://dx.doi.org/10.1016/0958-6946\(91\)90010-6](http://dx.doi.org/10.1016/0958-6946(91)90010-6).
28. Brüssow H, Fremont M, Bruttin A, Sidoti J, Constable A, Fryder V. Detection and classification of *Streptococcus thermophilus* bacteriophages isolated from industrial milk fermentation. Appl Environ Microbiol 1994; 60:4537-43; PMID:7811089.
29. Bruttin A, Desiere F, d'Amico N, Guérin J-P, Sidoti J, Huni B, et al. Molecular ecology of *Streptococcus thermophilus* bacteriophage infections in a cheese factory. Appl Environ Microbiol 1997; 63:3144-50; PMID:9251202.
30. Atamer Z, Ali Y, Neve H, Heller KJ, Hinrichs J. Thermal resistance of bacteriophages attacking flavor-producing dairy *Leuconostoc* starter cultures. Int Dairy J 2011; 21:327-34; <http://dx.doi.org/10.1016/j.idairyj.2010.11.005>.
31. Neve H, Kemper U, Geis A, Heller KJ. Monitoring and characterization of lactococcal bacteriophages in a dairy plant. Kieler Milchw Forsch 1994; 46:167-78.
32. Neve H, Dietrich J, Heller KJ. A short note on long-term stability of *Lactococcus lactis* bacteriophages in cheese brine. Kieler Milchwirtschaftliche Forschungsberichte 2005; 57:191-200.
33. Verreault D, Gendron L, Rousseau GM, Veillette M, Massé D, Lindsley WG, et al. Detection of airborne lactococcal bacteriophages in cheese manufacturing plants. Appl Environ Microbiol 2011; 77:491-7; PMID:21115712; <http://dx.doi.org/10.1128/AEM.01391-10>.
34. Verreault D, Moineau S, Duchaine C. Methods for sampling of airborne viruses. Microbiol Mol Biol Rev 2008; 72:413-44; PMID:18772283; <http://dx.doi.org/10.1128/MMBR.00002-08>.
35. Briggiler Marcó M, Quiberoni A, Negro AC, Reinheimer JA, Alfano OM. Evaluation of the photocatalytic inactivation efficiency of dairy bacteriophages. Chem Eng J 2011; 172:987-93; <http://dx.doi.org/10.1016/j.cej.2011.07.012>.
36. Kosikowski FV. Whey utilization and whey products. J Dairy Sci 1979; 62:1149-60; [http://dx.doi.org/10.3168/jds.S0022-0302\(79\)83389-5](http://dx.doi.org/10.3168/jds.S0022-0302(79)83389-5).
37. Brown RJ, Ernstrom CA. Incorporation of ultrafiltration concentrated whey solids into Cheddar cheese for increased yield. J Dairy Sci 1982; 65:2391-5; [http://dx.doi.org/10.3168/jds.S0022-0302\(82\)82514-9](http://dx.doi.org/10.3168/jds.S0022-0302(82)82514-9).
38. Matthews ME. Whey protein recovery process and products. J Dairy Sci 1984; 67:2680-92; [http://dx.doi.org/10.3168/jds.S0022-0302\(84\)81626-4](http://dx.doi.org/10.3168/jds.S0022-0302(84)81626-4).
39. Punidadas P, Feirtag J, Tung MA. Incorporating whey proteins into mozzarella cheese. Int J Dairy Technol 1999; 52:51-5; <http://dx.doi.org/10.1111/j.1471-0307.1999.tb02070.x>.
40. Hinrichs J. Incorporation of whey proteins in cheese. Int Dairy J 2001; 11:495-503; [http://dx.doi.org/10.1016/S0958-6946\(01\)00071-1](http://dx.doi.org/10.1016/S0958-6946(01)00071-1).
41. Atamer Z, Dietrich J, Neve H, Heller KJ, Hinrichs J. Influence of the suspension media on the thermal treatment of mesophilic lactococcal bacteriophages. Int Dairy J 2010; 20:408-14; <http://dx.doi.org/10.1016/j.idairyj.2009.12.014>.
42. Canchaya C, Proux C, Fournous G, Bruttin A, Brüssow H. Prophage genomics. Microbiol Mol Biol Rev 2003; 67:238-76; PMID:12794192; <http://dx.doi.org/10.1128/MMBR.67.2.238-276.2003>.
43. Séchaud L, Cluzel PJ, Rousseau M, Baumgartner A, Accolas JP. Bacteriophages of lactobacilli. Biochimie 1988; 70:401-10; PMID:3139059; [http://dx.doi.org/10.1016/0300-9084\(88\)90214-3](http://dx.doi.org/10.1016/0300-9084(88)90214-3).
44. Davidson BE, Powell IB, Hillier AJ. Temperate bacteriophages and lysogeny in lactic acid bacteria. FEMS Microbiol Rev 1990; 7:79-90; PMID:2271226.
45. Séchaud L, Rousseau M, Fayard B, Callegari ML, Quénez P, Accolas J-P. Comparative study of 35 bacteriophages of *Lactobacillus helveticus*: morphology and host range. Appl Environ Microbiol 1992; 58:1011-8; PMID:16348661.
46. Carminati D, Mazzucotelli L, Giraffa G, Neviani E. Incidence of inducible bacteriophage in *Lactobacillus helveticus* strains isolated from natural whey starter cultures. J Dairy Sci 1997; 80:1505-11; [http://dx.doi.org/10.3168/jds.S0022-0302\(97\)76079-X](http://dx.doi.org/10.3168/jds.S0022-0302(97)76079-X).
47. Josephsen J, Neve H. Bacteriophages and lactic acid bacteria. In: Salminen S, von Wright A, eds. Lactic Acid Bacteria. Microbiology and Functional Aspects. New York, USA: Marcel Dekker Inc. 1998; 385-436.
48. Ventura M, Zomer A, Canchaya C, O'Connell-Motherway M, Kuipers O, Turrioni F, et al. Comparative analyses of prophage-like elements present in two *Lactococcus lactis* strains. Appl Environ Microbiol 2007; 73:7771-80; PMID:17933937; <http://dx.doi.org/10.1128/AEM.01273-07>.

49. Suárez V, Zago M, Quiberoni A, Carminati D, Giraffa G, Reinheimer J. Lysogeny in *Lactobacillus delbrueckii* strains and characterization of two new temperate prolate-headed bacteriophages. *J Appl Microbiol* 2008; 105:1402-11; PMID:18713281; <http://dx.doi.org/10.1111/j.1365-2672.2008.03876.x>.
50. Sun X, Van Sinderen D, Moineau S, Heller KJ. Impact of lysogeny on bacteria with a focus on Lactic Acid Bacteria. In: Adams HT, ed. *Contemporary Trends in Bacteriophage Research*. New York, United States: Nova Science Publishers, Inc. 2009; 309-336.
51. Mercanti DJ, Carminati D, Reinheimer JA, Quiberoni A. Widely distributed lysogeny in probiotic lactobacilli represents a potentially high risk for the fermentative dairy industry. *Int J Food Microbiol* 2011; 144:503-10; PMID:21131090; <http://dx.doi.org/10.1016/j.ijfoodmicro.2010.11.009>.
52. Capra ML, Mercanti DJ, Reinheimer JA, Quiberoni AL. Characterisation of three temperate phages released from the same *Lactobacillus paracasei* commercial strain. *Int J Dairy Technol* 2010; 63:396-405; <http://dx.doi.org/10.1111/j.1471-0307.2010.00600.x>.
53. Durmaz E, Miller MJ, Azcarate-Peril MA, Toon SP, Klaenhammer TR. Genome sequence and characteristics of Lrm1, a prophage from industrial *Lactobacillus rhamnosus* strain M1. *Appl Environ Microbiol* 2008; 74:4601-9; PMID:18539811; <http://dx.doi.org/10.1128/AEM.00010-08>.
54. Shimizu-Kadota M, Kiwaki M, Hirokawa H, Tsuchida N. ISL1: a new transposable element in *Lactobacillus casei*. *Mol Gen Genet* 1985; 200:193-8; PMID:2993817; <http://dx.doi.org/10.1007/BF00425423>.
55. Moineau S, Pandian S, Klaenhammer TR. Evolution of a lytic bacteriophage via DNA acquisition from the *Lactococcus lactis* chromosome. *Appl Environ Microbiol* 1994; 60:1832-41; PMID:16349277.
56. Bouchard JD, Moineau S. Homologous recombination between a lactococcal bacteriophage and the chromosome of its host strain. *Virology* 2000; 270:65-75; PMID:10772980; <http://dx.doi.org/10.1006/viro.2000.0226>.
57. Shimizu-Kadota M, Kiwaki M, Sawaki S, Shirasawa Y, Shibahara-Sone H, Sako T. Insertion of bacteriophage phiFSW into the chromosome of *Lactobacillus casei* strain Shirota (S-1): characterization of the attachment sites and the integrase gene. *Gene* 2000; 249:127-34; PMID:10831846; [http://dx.doi.org/10.1016/S0378-1119\(00\)00154-2](http://dx.doi.org/10.1016/S0378-1119(00)00154-2).
58. Labrie SJ, Moineau S. Abortive infection mechanisms and prophage sequences significantly influence the genetic makeup of emerging lytic lactococcal phages. *J Bacteriol* 2007; 189:1482-7; PMID:17041060; <http://dx.doi.org/10.1128/JB.01111-06>.
59. Lortal S, Chapot-Chartier MP. Role, mechanisms and control of lactic acid bacteria lysis in cheese. *Int Dairy J* 2005; 15:857-71; <http://dx.doi.org/10.1016/j.idairyj.2004.08.024>.
60. Weinbauer MG. Ecology of prokaryotic viruses. *FEMS Microbiol Rev* 2004; 28:127-81; PMID:15109783; <http://dx.doi.org/10.1016/j.femsre.2003.08.001>.
61. Ackermann H-W. 5500 Phages examined in the electron microscope. *Arch Virol* 2007; 152:227-43; PMID:17051420; <http://dx.doi.org/10.1007/s00705-006-0849-1>.
62. Dupuis M-E, Moineau S. Genome organization and characterization of the virulent lactococcal phage 1358 and its similarities to *Listeria* phages. *Appl Environ Microbiol* 2010; 76:1623-32; PMID:20061452; <http://dx.doi.org/10.1128/AEM.02173-09>.
63. Samson JE, Moineau S. Characterization of *Lactococcus lactis* phage 949 and comparison with other lactococcal phages. *Appl Environ Microbiol* 2010; 76:6843-52; PMID:20802084; <http://dx.doi.org/10.1128/AEM.00796-10>.
64. Mata M, Trautwetter A, Luthaud G, Ritzenthaler P. Thirteen virulent and temperate bacteriophages of *Lactobacillus bulgaricus* and *Lactobacillus lactis* belong to a single DNA homology group. *Appl Environ Microbiol* 1986; 52:812-8; PMID:16347174.
65. Desiere F, Lucchini S, Canchaya C, Ventura M, Brüßow H. Comparative genomics of phages and prophages in lactic acid bacteria. *Antonie Van Leeuwenhoek* 2002; 82:73-91; PMID:12369206; <http://dx.doi.org/10.1023/A:1020676825358>.
66. Nelson D. Phage taxonomy: we agree to disagree. *J Bacteriol* 2004; 186:7029-31; PMID:15489416; <http://dx.doi.org/10.1128/JB.186.21.7029-7031.2004>.
67. Le Marrec C, van Sinderen D, Walsh L, Stanley E, Vlegels E, Moineau S, et al. *Streptococcus thermophilus* bacteriophages can be divided into two distinct groups based on mode of packaging and structural protein composition. *Appl Environ Microbiol* 2007; 63:3246-53.
68. Mills S, Griffin C, O' Sullivan O, Coffey A, McAuliffe OE, Meijer WC, et al. A new phage on the 'Mozzarella' block: bacteriophage 5093 shares a low level of homology with other *Streptococcus thermophilus* phages. *Int Dairy J* 2011; <http://dx.doi.org/10.1016/j.idairyj.2011.06.003>.
69. Brüßow H, Kutter E. Phage ecology. In: Kutter E, Sulakvelidze A, eds. *Bacteriophages. Biology and applications*. Boca Raton, FL, USA: CRC Press. 2005; 129-163.
70. Quiberoni A, Tremblay D, Ackermann H-W, Moineau S, Reinheimer JA. Diversity of *Streptococcus thermophilus* phages in a large-production cheese factory in Argentina. *J Dairy Sci* 2006; 89:3791-9; PMID:16960053; [http://dx.doi.org/10.3168/jds.S0022-0302\(06\)72420-1](http://dx.doi.org/10.3168/jds.S0022-0302(06)72420-1).
71. Sozzi T, Poulin JM, Maret R, Pousaz R. Isolation of a bacteriophage of *Leuconostoc mesenteroides* from dairy produce. *J Appl Bacteriol* 1978; 44:159-61; <http://dx.doi.org/10.1111/j.1365-2672.1978.tb00787.x>.
72. Shin C. Some characteristics of *Leuconostoc cremoris* bacteriophage isolated from blue cheese. *Jpn J Zotech Sci* 1983; 54:481-6.
73. Saxelin ML, Nurmiaho-Lassila EL, Meriläinen VT, Forsén RI. Ultrastructure and host specificity of bacteriophages of *Streptococcus cremoris*, *Streptococcus lactis* subsp. *diacetylatis* and *Leuconostoc cremoris* from Finnish fermented milk. *Appl Environ Microbiol* 1986; 52:771-7; PMID:16347170.
74. Davey GP, Ward LJH, Brown JCS. Characterisation of four *Leuconostoc* bacteriophages isolated from dairy fermentations. *FEMS Microbiol Lett* 1995; 128:21-5; <http://dx.doi.org/10.1111/j.1574-6968.1995.tb07494.x>.
75. Boizet B, Mata M, Mignot O, Ritzenthaler P, Sozzi T. Taxonomic characterization of *Leuconostoc mesenteroides* and *Leuconostoc oenos* bacteriophage. *FEMS Microbiol Lett* 1992; 90:211-6; <http://dx.doi.org/10.1111/j.1574-6968.1992.tb05154.x>.
76. Barrangou R, Yoon SS, Breidt Jr F Jr, Fleming HP, Klaenhammer TR. Characterization of six *Leuconostoc fallax* bacteriophages isolated from an industrial sauerkraut fermentation. *Appl Environ Microbiol* 2002; 68:5452-8; PMID:12406737; <http://dx.doi.org/10.1128/AEM.68.11.5452-5458.2002>.
77. Lu Z, Altermann E, Breidt F, Kozayvkin S. Sequence analysis of *Leuconostoc mesenteroides* bacteriophage Phi1-A4 isolated from an industrial vegetable fermentation. *Appl Environ Microbiol* 2010; 76:1955-66; PMID:20118355; <http://dx.doi.org/10.1128/AEM.02126-09>.
78. Sturino JM, Klaenhammer TR. Bacteriophage defense systems and strategies for lactic acid bacteria. *Adv Appl Microbiol* 2004; 56:331-78; PMID:15566985; [http://dx.doi.org/10.1016/S0065-2164\(04\)56011-2](http://dx.doi.org/10.1016/S0065-2164(04)56011-2).
79. Binetti A, Reinheimer JA, Álvarez MA. Dairy bacteriophages and bacteriophage resistance. In: Mayo B, López P, Gaspar Pérez-Martínez G, eds. *Molecular aspects of Lactic Acid Bacteria for traditional and new applications*. Research Signpost, Kerala, India 2008:209-234.
80. del Río B, Martín MC, Martínez N, Magadán AH, Álvarez MA. Multiplex Fast Real-Time Polymerase Chain Reaction for quantitative detection and identification of *cos* and *pac* *Streptococcus thermophilus* bacteriophages. *Appl Environ Microbiol* 2008; 74:4779-81; PMID:18539804; <http://dx.doi.org/10.1128/AEM.00295-08>.
81. Martín MC, del Río B, Martínez N, Magadán AH, Álvarez MA. Fast real-time polymerase chain reaction for quantitative detection of *Lactobacillus delbrueckii* bacteriophages in milk. *Food Microbiol* 2008; 25:978-82; PMID:18954733; <http://dx.doi.org/10.1016/j.fm.2008.07.004>.
82. Ly-Chatain MH, Durand L, Rigobello V, Vera A, Demarigny Y. Direct quantitative detection and identification of Lactococcal bacteriophages from milk and whey by Real-Time PCR: Application for the detection of Lactococcal bacteriophages in goat's raw milk whey in France. *Int J Microbiol* 2011; 2011:594369; <http://dx.doi.org/10.1155/2011/594369>; PMID:22013446.
83. Garneau JE, Moineau S. Bacteriophages of lactic acid bacteria and their impact on milk fermentations. *Microb Cell Fact* 2011; 10(Suppl 1):S20; PMID:21995802; <http://dx.doi.org/10.1186/1475-2859-10-S1-S20>.
84. IDF Starters in the manufacture of cheese. Bulletin 129 of the International Dairy Federation Brussels: International Dairy Federation 1980; 4-21.
85. Steenson LR, Klaenhammer TR. *Streptococcus cremoris* M12R transconjugants carrying the conjugal plasmid pTR2030 are insensitive to attack by lytic bacteriophages. *Appl Environ Microbiol* 1985; 50:851-8; PMID:3002270.
86. Michelsen O, Cuesta-Domínguez A, Albrechtsen B, Jensen PR. Detection of bacteriophage-infected cells of *Lactococcus lactis* by using flow cytometry. *Appl Environ Microbiol* 2007; 73:7575-81; PMID:17921265; <http://dx.doi.org/10.1128/AEM.01219-07>.
87. IDF. Practical phage control. Bulletin 263 of the International Dairy Federation Brussels: International Dairy Federation 1991; 29-39.
88. García-Aljaro C, Muñoz-Berbel X, Muñoz FJ. On-chip impedimetric detection of bacteriophages in dairy samples. *Biosens Bioelectron* 2009; 24:1712-6; PMID:18926694; <http://dx.doi.org/10.1016/j.bios.2008.08.047>.
89. Zago M, Scaltriti E, Fornasari ME, Rivetti C, Grolli S, Giraffa G, et al. Epifluorescence and atomic force microscopy: Two innovative applications for studying phage-host interactions in *Lactobacillus helveticus*. *J Microbiol Methods* 2012; 88:41-6; PMID:22024504; <http://dx.doi.org/10.1016/j.mimet.2011.10.006>.
90. Coffey A, Ross RP. Bacteriophage-resistance systems in dairy starter strains: molecular analysis to application. *Antonie Van Leeuwenhoek* 2002; 82:303-21; PMID:12369198; <http://dx.doi.org/10.1023/A:1020639717181>.
91. Moineau S, Tremblay D, Labrie S. Phages of lactic acid bacteria: from genomics to industrial applications. *ASM News* 2002; 68:388-93.
92. Heap HA, Harnett JT. Bacteriophage in the dairy industry. In: Roginski H, Fuquay JW, Fox PF, eds. *Encyclopedia of dairy sciences*. Academic Press, Elsevier Science, USA 2003; 36-142.
93. Guglielmotti DM, Mercanti DJ, Reinheimer JA, Quiberoni Adell L. Review: efficiency of physical and chemical treatments on the inactivation of dairy bacteriophages. *Front Microbiol* 2011; 2:282; PMID:22275912.

94. Ebrecht AC, Guglielmotti DM, Tremmel G, Reinheimer JA, Suárez VB. Temperate and virulent *Lactobacillus delbrueckii* bacteriophages: comparison of their thermal and chemical resistance. *Food Microbiol* 2010; 27:515-20; PMID:20417401; <http://dx.doi.org/10.1016/j.fm.2009.12.012>.
95. Mercanti DJ, Guglielmotti DM, Patrignani F, Reinheimer JA, Quiberoni A. Resistance of two temperate *Lactobacillus paracasei* bacteriophages to high pressure homogenization, thermal treatments and chemical biocides of industrial application. *Food Microbiol* 2012; 29:99-104; PMID:22029923; <http://dx.doi.org/10.1016/j.fm.2011.09.003>.
96. Kakita Y, Obuchi E, Nakano K, Murata K, Kuroiwa A, Miake F, et al. Photocatalytic inactivation of *Lactobacillus* PL-1 phage by a thin of titania. *Biocontrol Sci* 2000; 5:73-9; <http://dx.doi.org/10.4265/bio.5.73>.
97. Kashige N, Kakita Y, Nakashima Y, Miake F, Watanabe K. Mechanism of the photocatalytic inactivation of *Lactobacillus casei* phage PL-1 by titania thin film. *Curr Microbiol* 2001; 42:184-9; PMID:11270652; <http://dx.doi.org/10.1007/s002840010201>.
98. Koziumi Y, Taya M. Kinetic evaluation of biocidal activity of titanium dioxide against phage MS-2 considering interaction between the phage and photocatalyst particles. *Biochem Eng J* 2002; 12:107-16; [http://dx.doi.org/10.1016/S1369-703X\(02\)00046-3](http://dx.doi.org/10.1016/S1369-703X(02)00046-3).
99. Kühn KP, Chaberny IF, Massholder K, Strickler M, Benz VW, Sonntag HG, et al. Disinfection of surfaces by photocatalytic oxidation with titanium dioxide and UVA light. *Chemosphere* 2003; 53:71-7; PMID:12892668; [http://dx.doi.org/10.1016/S0045-6535\(03\)00362-X](http://dx.doi.org/10.1016/S0045-6535(03)00362-X).
100. Cho M, Chung H, Choi W, Yoon J. Different inactivation behaviors of MS-2 phage and *Escherichia coli* in TiO₂ photocatalytic disinfection. *Appl Environ Microbiol* 2005; 71:270-5; PMID:15640197; <http://dx.doi.org/10.1128/AEM.71.1.270-275.2005>.
101. Pal A, Pehkonen SO, Yu LE, Ray MB. Photocatalytic inactivation of Gram-positive and Gram-negative bacteria using fluorescent light. *J Photochem Photobiol A* 2007; 186:335-41; <http://dx.doi.org/10.1016/j.jphotochem.2006.09.002>.
102. Ditra IB, Steele A, Liprot C, Tobin J, Tyler H, Yates HM, et al. Photocatalytic antimicrobial activity of thin surface films of TiO₂(2), CuO and TiO₂(2)/CuO dual layers on *Escherichia coli* and bacteriophage T4. *Appl Microbiol Biotechnol* 2008; 79:127-33; PMID:18317747; <http://dx.doi.org/10.1007/s00253-008-1411-8>.
103. Zacarias SM, Vaccari MC, Alfano OM, Irazoqui HA, Imoberdorf GE. Effect of the radiation flux on the photocatalytic inactivation of spores of *Bacillus subtilis*. *J Photochem Photobiol A* 2010; 214:171-80; <http://dx.doi.org/10.1016/j.jphotochem.2010.06.021>.
104. Kover Synergy. UV Sterile Air System. Available at: http://www.koveritalia.com/uv_steril_air_system.htm; 2012.
105. Novapure. Air Titan Air Purifiers. Available at: <http://www.morphicenvirotech.com/novapure/>; 2012.
106. Atamer Z, Hinrichs J. Thermal inactivation of the heat-resistant *Lactococcus lactis* bacteriophage P680 in modern cheese processing. *Int Dairy J* 2010; 20:163-8; <http://dx.doi.org/10.1016/j.idairyj.2009.09.006>.
107. Moroni O, Jean J, Autret J, Fliss I. Inactivation of lactococcal bacteriophages in liquid media using dynamic high pressure. *Int Dairy J* 2002; 12:907-13; [http://dx.doi.org/10.1016/S0958-6946\(02\)00118-8](http://dx.doi.org/10.1016/S0958-6946(02)00118-8).
108. Diels AMJ, Michiels CW. High-pressure homogenization as a non-thermal technique for the inactivation of microorganisms. *Crit Rev Microbiol* 2006; 32:201-16; PMID:17123905; <http://dx.doi.org/10.1080/10408410601023516>.
109. Capra ML, Patrignani F, Quiberoni A, Reinheimer JA, Lanciotti R, Guerzoni ME. Effect of high pressure homogenization on lactic acid bacteria phages and probiotic bacteria phages. *Int Dairy J* 2009b; 19:336-41; <http://dx.doi.org/10.1016/j.idairyj.2008.11.002>.
110. D'Souza DH, Su X, Roach A, Harte F. High-pressure homogenization for the inactivation of human enteric virus surrogates. *J Food Prot* 2009; 72:2418-22; PMID:19903411.
111. Patterson MF. Microbiology of pressure-treated foods. *J Appl Microbiol* 2005; 98:1400-9; PMID:15916652; <http://dx.doi.org/10.1111/j.1365-2672.2005.02564.x>.
112. Müller-Merbach M, Rauscher T, Hinrichs J. Inactivation of bacteriophages by thermal and high-pressure treatment. *Int Dairy J* 2005b; 15:777-84; <http://dx.doi.org/10.1016/j.idairyj.2004.08.019>.
113. Lyne J. Technological importance in the dairy industry. In: Fuquay J, Fox P, McSweeney P, eds. *Encyclopedia of dairy science*, 2^o Edition (Volume 1), Academic Press, Elsevier Science, USA 2011; 439-444.
114. Hicks CL, Clark-Safko PA, Surjawan I, O'Leary J. Use of bacteriophage derived peptides to delay phage infections. *Food Res Int* 2004; 37:115-22; <http://dx.doi.org/10.1016/j.foodres.2003.09.009>.
115. Bissonnette F, Labrie S, Deveau H, Lamoureux M, Moineau S. Characterization of mesophilic mixed starter cultures used for the manufacture of aged cheddar cheese. *J Dairy Sci* 2000; 83:620-7; PMID:10791775; [http://dx.doi.org/10.3168/jds.S0022-0302\(00\)74921-6](http://dx.doi.org/10.3168/jds.S0022-0302(00)74921-6).
116. Labrie SJ, Samson JE, Moineau S. Bacteriophage resistance mechanisms. *Nat Rev Microbiol* 2010; 8:317-27; PMID:20348932; <http://dx.doi.org/10.1038/nrmicro2315>.
117. Klaenhammer TR, Fitzgerald GF. Bacteriophage and bacteriophage-resistance. In: Gasson MJ, de Vos WM, eds. *Genetics and Biotechnology of Lactic Acid Bacteria*. Blackie Academic and Professional, Glasgow 1994; 106-168.
118. Limsowtink K, Terzaghi BE. Phage resistant mutants: their selection and use in cheese factories. *NZ J Dairy Sci Tech* 1976; 11:251-6.
119. Weimer BC, Blake M, Hillier AJ, Davidson BE. Studies on the isolation of phage-resistant derivatives of *Lactococcus lactis* subsp. *cremoris* FG2 with phage sk1. *Aust J Dairy Technol* 1993; 48:59-61.
120. Viscardi M, Capparelli R, Di Matteo R, Carminati D, Giraffa G, Iannelli D. Selection of bacteriophage-resistant mutants of *Streptococcus thermophilus*. *J Microbiol Methods* 2003; 55:109-19; PMID:14500002; [http://dx.doi.org/10.1016/S0167-7012\(03\)00146-5](http://dx.doi.org/10.1016/S0167-7012(03)00146-5).
121. Barrangou R, Fremaux C, Deveau H, Richards M, Boyaval P, Moineau S, et al. CRISPR provides acquired resistance against viruses in prokaryotes. *Science* 2007; 315:1709-12; PMID:17379808; <http://dx.doi.org/10.1126/science.1138140>.
122. Binetti AG, Bailo NB, Reinheimer JA. Spontaneous phage-resistant mutants of *Streptococcus thermophilus*: Isolation and technological characteristics. *Int Dairy J* 2007a; 17:343-9; <http://dx.doi.org/10.1016/j.idairyj.2006.05.002>.
123. Deveau H, Barrangou R, Garneau JE, Labonté J, Fremaux C, Boyaval P, et al. Phage response to CRISPR-encoded resistance in *Streptococcus thermophilus*. *J Bacteriol* 2008; 190:1390-400; PMID:18065545; <http://dx.doi.org/10.1128/JB.01412-07>.
124. Neviani E, Carminati D, Giraffa G. Selection of some bacteriophage- and lysozyme-resistant variants of *Lactobacillus helveticus* CNRZ 892. *J Dairy Sci* 1992; 75:905-13; [http://dx.doi.org/10.3168/jds.S0022-0302\(92\)77830-8](http://dx.doi.org/10.3168/jds.S0022-0302(92)77830-8).
125. Carminati D, Zennaro R, Neviani E, Giraffa G. Selezione e caratteristiche di mutanti fago-resistenti di *L. helveticus*. *Sci Tecn Latt Cas* 1993; 44:33-48.
126. Reinheimer JA, Morelli R, Callegari ML, Bottazzi V. Phage resistance in *Lactobacillus helveticus* CNRZ 328. *Microbiol Alim Nutr* 1993; 11:235-40.
127. Quiberoni A, Reinheimer JA, Tailliez P. Characterization of *Lactobacillus helveticus* phage-resistant mutants by RAPD fingerprints and phenotypic parameters. *Food Res Int* 1998a; 31:537-42; [http://dx.doi.org/10.1016/S0963-9969\(99\)00020-4](http://dx.doi.org/10.1016/S0963-9969(99)00020-4).
128. Guglielmotti DM, Reinheimer JA, Binetti AG, Giraffa G, Carminati D, Quiberoni A. Characterization of spontaneous phage-resistant derivatives of *Lactobacillus delbrueckii* commercial strains. *Int J Food Microbiol* 2006; 111:126-33; PMID:16884802; <http://dx.doi.org/10.1016/j.ijfoodmicro.2006.04.035>.
129. Capra ML, Mercanti DJ, Rossetti LC, Reinheimer JA, Quiberoni A. Isolation and phenotypic characterization of *Lactobacillus casei* and *Lactobacillus paracasei* bacteriophage-resistant mutants. *J Appl Microbiol* 2011; 111:371-81; PMID:21599814; <http://dx.doi.org/10.1111/j.1365-2672.2011.05056.x>.
130. Valyasevi R, Sandine WE, Geller BL. A membrane protein is required for bacteriophage c2 infection of *Lactococcus lactis* subsp. *lactis* C2. *J Bacteriol* 1991; 173:6095-100; PMID:1917843.
131. Chapot-Chartier MP, Vinogradov E, Sadovskaya I, Andre G, Mistou MY, Trieu-Cuot P, et al. Cell surface of *Lactococcus lactis* is covered by a protective polysaccharide pellicle. *J Biol Chem* 2010; 285:10464-71; PMID:20106971; <http://dx.doi.org/10.1074/jbc.M109.082958>.
132. Haaber J, Moineau S, Fortier L-C, Hammer K. AbiV, a novel antiphage abortive infection mechanism on the chromosome of *Lactococcus lactis* subsp. *cremoris* MG1363. *Appl Environ Microbiol* 2008; 74:6528-37; PMID:18776030; <http://dx.doi.org/10.1128/AEM.00780-08>.
133. Sturino JM, Klaenhammer TR. Engineered bacteriophage-defence systems in bioprocessing. *Nat Rev Microbiol* 2006; 4:395-404; PMID:16715051; <http://dx.doi.org/10.1038/nrmicro1393>.
134. Watanabe K, Takesue S, Jin-Nai K, Yoshikawa T. Bacteriophage active against the lactic acid beverage-producing bacterium *Lactobacillus casei*. *Appl Microbiol* 1970; 20:409-15; PMID:4991958.
135. Forsman P, Tanskanen J, Alatossava T. Structural similarity and genetic homology between *Lactobacillus casei* bacteriophages isolated in Japan and in Finland. *Biosci Biotechnol Biochem* 1993; 57:2043-8; <http://dx.doi.org/10.1271/bbb.57.2043>.
136. Saarela M, Mogensen G, Fondén R, Mättö J, Mattila-Sandholm T. Probiotic bacteria: safety, functional and technological properties. *J Biotechnol* 2000; 84:197-215; PMID:11164262; [http://dx.doi.org/10.1016/S0168-1656\(00\)00375-8](http://dx.doi.org/10.1016/S0168-1656(00)00375-8).
137. Capra ML, Del L, Quiberoni A, Ackermann HW, Moineau S, Reinheimer JA. Characterization of a new virulent phage (MLC-A) of *Lactobacillus paracasei*. *J Dairy Sci* 2006; 89:2414-23; PMID:16772557; [http://dx.doi.org/10.3168/jds.S0022-0302\(06\)72314-1](http://dx.doi.org/10.3168/jds.S0022-0302(06)72314-1).