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Arcobacter butzleri: Up-to-date taxonomy, ecology, and pathogenicity of an emerging pathogen

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Abstract

Arcobacter butzleri, recently emended to the *Aliarcobacter butzleri* comb. nov., is an emerging pathogen causing enteritis, severe diarrhea, septicaemia, and bacteraemia in humans and enteritis, stillbirth, and abortion in animals. Since its recognition as emerging pathogen on 2002, advancements have been made in elucidating its pathogenicity and epidemiology, also thanks to advent of genomics, which, moreover, contributed in emending its taxonomy. In this review, we provide an overview of the up-to-date taxonomy, ecology, and pathogenicity of this emerging pathogen. Moreover, the implication of *A. butzleri* in the safety of foods is pinpointed, and culture-dependent and independent detection, identification, and typing methods as well as strategies to control and prevent the survival and growth of this pathogen are provided.

KEYWORDS

Aliarcobacter butzleri, *Arcobacter butzleri*, food safety, meat, milk and dairy, shellfish, vegetables

1 | *ALIARCOBACTER BUTZLERI* TAXONOMY

Genomic approaches of the latest years have deeply contributed to amend the taxonomy of the genus *Arcobacter*, so named on 1991 (Vandamme et al., 1991) from the Latin "arc-shaped bacterium" as bacteria belonging to this genus are usually helical, curved, or "S"-shaped.

The current validated taxonomy of *Arcobacter* places this genus within the *Campylobacteraceae* family (belonging to the class *Epsilonproteobacteria* of the phylum *Proteobacteria*) together with the *Campylobacter* and *Sulfurospirillum* genera. As the result of a recently performed comparative genomic analysis, Waite et al. (2017, 2018) proposed a reclassification of the class *Epsilonproteobacteria* to *Campylobacteria*, based on which the genus *Arcobacter* should be placed into the *Arcobacteraceae* fam. nov. (type genus: *Arcobacter*, order: *Campylobacterales*, class: *Campylobacteria*, class. nov., phylum: *Campylobacterota* phyl. nov. (Waite et al., 2017, 2018).

This genus comprises to date 29 recognized species (Ferreira, Oleastro, & Domingues, 2019), but this number is rapidly increasing: indeed, only in the last 2 years four potentially novel species have been described: *A. canalis* sp. nov., isolated from a water canal contaminated with urban sewage (Pérez-Cataluña, Salas-Massó, & Figueras, 2018b), *A. lacus* sp. nov, and *A. caeni* sp. nov., isolated from reclaimed water (Pérez-Cataluña, Salas-Massó, & Figueras, 2018c), and *Arcobacter peruensis* sp. nov. described by Callbeck et al. in (2019) and isolated from sulfide- and organic-rich coastal waters.

In 2018 Pérez-Cataluña et al. (2018a) revisited the taxonomy of the genus *Arcobacter* using the core genome of 57 strains (286 genes), a multilocus sequence analysis with 13 housekeeping genes, and genomic indexes like average nucleotide identity (ANI), *in silico* DNA–DNA hybridization (*is*DDH), average amino-acid identity (AAI), percentage of conserved proteins, and relative synonymous codon usage.

Following the suggestion of Diéguez, Balboa, Magnesen, and Romalde (2017), that certain species of this genus might be reassigned to other genera considering the low 16S rRNA similarity (below the 95% cutoff; Diéguez et al., 2017), and based on the results obtained, the authors proposed the division of the current genus *Arcobacter* into seven different genera: *Arcobacter*, *Aliiarcobacter* gen. nov., *Pseudoarcobacter* gen. nov., *Haloarcobacter* gen. nov., *Malacobacter* gen. nov.,

Poseidonibacter gen. nov., and the candidate "*Arcomarinus*" gen. nov.

Aliiarcobacter gen. nov. (Pérez-Cataluña et al., 2018a), thereafter corrected to *Aliarcobacter* gen. nov. (Pérez-Cataluña et al., 2019a, 2019b), was described as including the eight following species: *Aliarcobacter cryaerophilus* comb. nov., *A. butzleri* comb. nov., *A. skirrowii* comb. nov., *A. cibarius* comb. nov., *A. thereius* comb. nov., *A. trophiarum* comb. nov., *A. lanthieri* comb. nov., and *A. faecis* comb. nov (Pérez-Cataluña et al., 2019a, 2019b). The type species of the genus *Aliarcobacter* gen. nov. is *A. cryaerophylus*.

The description of the species *Aliarcobacter butzleri* is the same given by Vandamme et al. (1992b) and the type strain is LMG 10828T (= CDC D2686T = ATCC 49616T).

The phylogenetic tree based on 13 housekeeping genes places *A. butzleri* species within the same subcluster of *A. lacus* RW43-9, with a 16S similarity of 99.9%, a multilocus sequence analysis (MLSA) value of 96.9%, ANI of 94.2%, *is*DDH of 55.7%, well differentiated from the other subcluster which includes the other *Aliarcobacter* species of the genus.

A. butzleri strains have been isolated from different matrices, including meat, vegetables, dairy, etc. indicating the ability to adapt to a wide range of ecological conditions. These capabilities are defined by the metabolic properties acquired during the evolution by a pangenome diversity (7,474 genes) highlighted by Isidro et al. (2020).

Recently, a taxogenomic analysis performed by Fanelli et al. (2020) on 20 *A. butzleri* genomes, based on 16S rRNA gene sequence analysis, multilocus sequence typing (MLST) on the 13 housekeeping genes used by Pérez-Cataluña et al. (2018a), ANI, AAI, DDH, and RAxML genome-based analysis, suggested the possibility to define, within *A. butzleri*, different subspecies reflecting the source of isolation. However, this hypothesis needs to be supported by the availability of a wider number of *A. butzleri* genomes, which should be isolated from different ecological niches, sequenced, and analyzed.

2 | DESCRIPTION OF *ALIARCOBACTER* GENUS AND *ALIARCOBACTER BUTZLERI* COMB. NOV

Cells of the *Aliarcobacter* (A.li.ar.co.bac'ter. L. pronoun *alius* other, another; N.L. masc. n. *Arcobacter* a bacterial generic name; N.L. masc. n. *Aliarcobacter* the other *Arcobacter*) genus are Gram-negative, curved rods 0.2 to 0.5 μm in diameter and 1 to 3 μm long. Moreover, they do not swarm but are motile by a single polar flagellum and do not produce fluorescent pigments. Chemoorganotrophic, oxidase and catalase positive, grow at 15 to 42 °C but not at 4% NaCl, in 2,3,5-triphenyltetrazolium chloride (TTC) (0.04%, wt/vol) or glycine (1% wt/vol), whereas some species of this genus may grow in safranin (0.05% wt/vol) or oxgall (1% wt/vol). *Aliarcobacter* cells do not ferment carbohydrates whereas reduce nitrate to nitrite. They hydrolyze indoxyl acetate but not urease. Some species are sensitive to cefoperazone (64 mg/L). Range of DNA G+C content is 26.4 to 29.4 mol%. The type species is *Aliarcobacter cryaerophilus* (Pérez-Cataluña et al., 2018a, 2019b).

The description of the *Aliarcobacter butzleri* comb. nov. (Pérez-Cataluña et al., 2018a, 2019a, 2019b), whose type strain has been confirmed to be LMG 10828^T (ATCC 49616^T, RM4018), has been consolidated to be the one proposed by Vandamme et al. (1992b). According to the latter, cells of this species are 0.2 to 0.4 μm wide and 1 to 3 μm long. On blood agar plates after 3 days of incubation, colonies have 2 to 4 mm diameter and most are round and whitish. Apart from the characteristics of the genus to which they belong, cells of *A. butzleri* have a weak catalase activity and grow in the presence of 8% glucose. All strains reduce nitrate and grow on VB medium and MacConkey agar, whereas 11 of the 12 tested strains by Vandamme et al. (1992b) produce DNase while 10 of 12 strains grow in the presence of 1.5% NaCl. Eight of the 12 strains tested grow at 42 °C, while three of 12 strains tested produce hydrogen sulfide from cysteine. Five of the 12 tested strains grow in the presence of 1% oxgall and in the presence of 3.5% NaCl, whereas 7 of the 12 strains tested grow in the presence of 1% glycine. Eight of the 12 tested strains grow in the presence of 0.04% TTC, 11 of 12 tested strains are susceptible to nalidixic acid and 10 of 12 strains tested are resistant to cephalothin (30 μg disks). Moreover, according to Vandamme et al. (1992b), *A. butzleri* has a DNA base composition of 28 to 29 mol%. Major fatty acids are 12:0, 14:0 3OH, 16:1 cis 9, 16:1 trans 9, 16:0, and 18:1 cis 11, whereas in smaller quantities are present 14:1 cis 7 and 14:0 (Vandamme et al., 1992b). Apart from one strain, which was isolated from spoiled meat, the remaining 11 strains tested by Vandamme et al. (1992b) were isolated from diarrheic feces of humans and animals, aborted fetuses, human blood, deadborn piglets, the eye of aborted porcine fetus, and from bovine liver. Thus, an exiguous number of strains was tested to assess the main phenotypic traits of this species and none of the strains used was isolated from water and food matrices such as shellfish, vegetables, milk and dairy products where they are being found with a high prevalence.

Further information has been recently provided by Fanelli et al. (2019, 2020) who performed a genomic and phenotypic characterization of strains isolated from shellfish and vegetables and from Isidro et al. (2020) who made a comparative genomic analysis of 49 *A. butzleri* strains isolated from different environments. In particular, the genome size of *A. butzleri* ranges from 2.07 to 2.58 Mbp, with a mean GC content of 26.9% (Isidro et al., 2020). Based on the protein functional

classification, the strains isolated from vegetables in the same geographic area shared the same distribution of clusters of orthologous groups (COGs) with a prevalence of the cluster "inorganic ion transport and metabolism," consistent with the lithotrophic nature of *Aliarcobacter* spp., which is more accentuated in plant-associated strains of the *A. butzleri* species (Fanelli et al., 2020). On the other hand, the strains isolated from shellfish revealed the prevalence, among COG categories, of the signal transduction mechanism cluster, followed by amino acid transport and metabolism cluster, cell wall/membrane/envelope biogenesis cluster and energy production and conversion cluster (Fanelli et al., 2019). Therefore, these strains have a versatile sensory transduction system and for energy and carbon they mostly rely on amino acid catabolism rather than on sugar fermentation, which is consistent with their origin (Fanelli et al., 2020). The metabolic fingerprinting obtained by using the Biolog AN MicroPlates^{TM} (Fanelli et al., 2020) confirmed the incapacity of the *A. butzleri* strains to metabolize carbohydrates described by Vandamme et al. (1992b), while they were able to utilize org

anic acids and amino acids as carbon sources. Overall, the following substrates were utilized by the tested *A. butzleri* strains, albeit with some differences: acetic acid, formic acid, fumaric acid, α-hydroxybutyric acid, itaconic acid, α-ketobutyric acid, D,L-lactic acid, L-lactic acid, D-lactic acid methyl ester, L-malic acid, propionic acid, pyruvic acid, pyruvic acid methyl ester, succinamic acid, succinic acid, succinic acid mono-methyl ester, L-alanyl-L-histidine, L-glutamic acid, L-glutamine, and L-threonine (Fanelli et al., 2020). All the strains used α-hydroxybutyric acid, D,L-lactic acid, D-lactic acid methyl ester, L- malic acid, pyruvic acid, succinic acid, and succinic acid mono-methyl ester, while only one of the five strains tested metabolized succinamic acid and L-glutamine. Otherwise L-alanyl-L-histidine was utilized only by *A. butzleri* LMG10828^{T} (Fanelli et al., 2020). Altogether, the tested *A. butzleri* strains did used 16 (Ab 39_O), 15 (Ab 55), 14 (LMG10828^{T}), 13 (Ab 6V), and 12 (Ab 34_O) of the listed substrates (Fanelli et al., 2020), with *A. butzleri* 39_O and 34_O as the most and the least metabolically versatile strains, respectively.

3 | ECOLOGY OF *A. BUTZLERI*

Various and numerous ecological niches are inhabited by *A. butzleri*, including environmental water sources (Table 1), raw and ready-to-eat foods such as vegetables (Table 2), and animal and food products of animal origin (Table 3) such as meat, milk, and cheese, fish and seafoods (Table 4). The presence and persistence of *A. butzleri* in the environment (Ferreira, Júlio, Queiroz, Domingues, & Oleastro, 2014a; Giacometti et al., 2013a, 2013b, 2015a; Hausdorf et al., 2013a; Piva et al., 2017; Rathlavath et al., 2017a; Scarano et al., 2014; Serraino & Giacometti, 2014) gained by its ability to form biofilms (Ferreira, Fraqueza, Queiroz, Domingues, & Oleastro, 2013; Girbau et al., 2017) and combined with its demonstrated survival in numerous and different water and food matrices/environments under various conditions (Badilla-Ramìrez, Fallas-Padilla, Fernàndez-Jaramillo, & Arias-Echandi, 2016; Balamurugan, Ahmed, & Chambers, 2013; Cervenka, 2007; Collins, Murano, & Weslwy, 1996; Fera et al., 2008; Fisher, Rowe, & Phillips, 2007; Giacometti et al., 2014, 2015b; Hausdorf et al., 2013b; Irkin, Abay, & Aydin, 2011; Kjeldgaard, Jørgensen, & Ingmer, 2009; Lee & Choi, 2012, 2013; Long & Phillips, 2003; Serraino et al., 2013b; Šilha, Vytřasová, Beňová, & Moťková, 2013) favor its spread and transmission within the different food chains (Ferreira et al., 2019; Shange, Gouws, & Hoffman, 2019). High occurrence of *A. butzleri* is being revealed in food-producing animals (Tables 3 and 4) suggesting them as important reservoir for this pathogen, thus implying successful colonization of the gastrointestinal tract at primary production and contamination during the slaughter process (Shange et al., 2019). The contamination of the food products of animal origin, especially poultry meat and meat products that are being found as sources of *A. butzleri* infection, can therefore be due to improper hygienic practices. In the last two decades, *A. butzleri* is being detected with a low to high prevalence in milk and dairy products (Table 3) as well as in their environment of production (De Cesare et al., 2016; Ferreira, Oleastro, & Domingues, 2017; Giacometti et al., 2013a, 2013b, 2015a; Piva et al., 2017; Scarano et al., 2014; Serraino & Giacometti, 2014; Serraino et al., 2013a; Tremonte et al., 2014). Moreover, its survival and growth in raw, pasteurized, and ultrahigh-temperature milk (Giacometti et al., 2014) and to the stress encountered during the production and storage of ricotta cheese (Giacometti et al., 2015b) and artisan water buffalo mozzarella cheese (Serraino et al., 2013b) have been demonstrated. These findings led to consider *A. butzleri* one of the emerging pathogens in milk and dairy products/environments of the 21st century (Fusco et al., 2020). Other sources of *A. butzleri* are pets, mainly dogs and cats (who have been indicated as significant reservoir for human infection with *A. butzleri* for their close contacts with owners [Goni et al., 2017]), wildlife (Wesley & Schroeder-Tucker, 2011), and zoo animals (Stirling et al., 2008), whereas few studies have demonstrated the presence of *A. butzleri* in the stools of healthy asymptomatic humans (Samie, Obi, Barrett, Powell, & Guerrant, 2007; Webb et al., 2016).

Apart from raw milk and cheeses, other foods that usually are consumed raw such as vegetables have been found to carry *A. butzleri* (Table 2) and strains isolated from this matrices have been demonstrated to possess many virulence and antibiotic resistance genes (Fanelli et al., 2020), suggesting that they can be another route of transmission of this pathogen. Its persistence in plants is gained by its ability to

TABLE 1 Excerpt of studies on the occurrence of *A. butzleri* in different water

Habitat/source	Country	Reference
Wastewater sewage	UK	Merga et al. (2014)
Wastewater effluent	Spain	Gonzàlez, Botella, Montes, Moreno, and Ferrus (2007)
Wastewater sewage	Spain	Collado, Inza, Guarro, and Figueras (2008)
Wastewater sludge	Spain	Collado et al. (2008)
Wastewater sewage	South Africa	Diergaardt, Venter, Spreeth, Theron, and Brözel (2004)
Sea water	Spain	Collado et al. (2008)
Sea water	Iran	Ghane (2014)
Lakes	Spain	Collado et al. (2008)
River	Spain	Collado et al. (2010)
Surface water	South Africa	Diergaardt et al. (2004)
Recreational water	USA	Lee, Agidi, Marion, and Lee (2012)
Drinking water	Turkey	Ertas, Dogruer, Gonulalan, Guner, and Ulger (2010)
Spring water	Turkey	Ertas et al. (2010)
Groundwater	USA	Rice, Rodgers, Wesley, Johnson, and Tanner (1999)
Waste and river water	Czech Republic	Šilha, Vacková, and Šilhová (2019)
Sewage, spring, and river water	Turkey	Talay, Molva, and Atabay (2016)
Surface water samples	Canada	Webb, Taboada, Selinger, Boras, and Inglis (2017)
Creek water	India	Laishram, Rathlavath, Lekshmi, Kumar, and Nayak (2016)
Coastal water	India	Rathlavath, Kumar, and Nayak (2017a)

TABLE 2 Excerpt of studies on the occurrence of *A. butzleri* in vegetables

Habitat/source	Country	Reference
Lettuce	Spain	González and Ferrús (2011)
Ready-to-eat packaged vegetables	Portugal	Vicente-Martins et al. (2018)
Fresh lettuce, celery, parsley, artichokes	Italy	Di Noto et al. (2018)
Leady green vegetables (lettuce, napa cabbage, spinach)	Korea	Kim et al. (2019)
Pre-cut ready-to-eat-vegetables (lettuce, spinach, rocket and valerian)	Italy	Mottola et al. (2016a)
Vegetables from retail shops and local vendors	India	Ramees et al. (2018)
Fresh vegetable (lettuce, spinach, and chard)	Spain	González, Bayas Morejón, and Ferrús (2017)

(i) survive on plastic, stainless steel, and glass surfaces (Cervenka et al., 2008; Šilha, Hrušková, Brožková, Moťková, & Vytřasová, 2014), (ii) form biofilm (Ferreira et al., 2013; Girbau et al., 2017), (iii) survive to scalding process conditions (Ho, Lipman, & Gaastra, 2008), (iv) tolerate biocides (Rasmussen, Kjeldgaard, Christensen, & Ingmer, 2013), (v) survive to sanitizing procedures (Hausdorf et al., 2013b; Rasmussen et al., 2013; Scarano et al., 2014; Šilha, Šilhová, Vytřasová, Brožková, & Pejchalová, 2016), and (vi) multiply under chilled conditions (Kjeldgaard et al., 2009). However, only few studies focusing on the occurrence of *A. butzleri* in vegetables have been carried out so far. Further studies are needed to assess the actual risk of this pathogen in vegetables.

Few studies to assess the occurrence of this species in fish are available so far. Nevertheless, *A. butzleri* is the most common species in bivalve molluscs (mussels, clams, oysters, etc.) (Table 4), most likely due to capture by the filter feeding process of bivalves and to a fecal contamination of the relevant environment (Fanelli et al., 2019). Indeed, Leoni et al. (2017) proposed *A. butzleri* as index organism for contamination in bivalve molluscs, which seem to be a reservoir of this pathogen.

Therefore, contaminated (especially if raw or undercooked) shellfish consumption may provoke *A. butzleri* infections in humans (Fanelli et al., 2019).

Even though latest genomic and phenotypic studies are providing novel insights into the antibiotic resistance and virulence of food-related *A. butzleri* strains (Fanelli et al., 2019, 2020; Isidro et al., 2020), further studies are needed to clarify the role of genetic endowment as well as of the food matrices the strain come from in the pathogenesis of *A. butzleri* disease and to allow the assessment and management of the food safety risks.

TABLE 3 Excerpt of studies on the occurrence of *A. butzleri* in animals and foods of animal origin

Habitat/source	Country	Reference
Poultry and beef	UK	Scullion, Harrington, and Madden (2006)
Chicken breast meat	Costa Rica	Fallas-Padilla, Rodrìguez-Rodrìguez, Jaramillo, and Echandi (2014)
Chicken meat	Australia	Rivas, Fegan, and Vanderlinde (2004)
Chicken	Korea	Lee et al. (2010)
Chicken, duck, geese, partridge, ostrich, quail, and meat	Iran	Rahimi (2014)
Chicken	Korea	Lee et al. (2012)
Chicken, pork, and beef	Spain	Nieva-Echevarria, Martinez-Malaxetxebarria, Girbau, Alonso, and Fernández-Astorga (2013)
Chicken	India	Sekhar, Tumati, Chinnam, Kothapalli, and Sharif (2018)
Chicken (fecal samples)	Chile	Fernàndez, Villanueva, Mansilla, Gonzalez, and Latif (2015)
Chicken (cloaca swabs fecal samples)	Costa Rica	Bogantes, Fallas-Padilla, Rodríguez-Rodríguez, Fernández-Jaramillo, and Arias-Echandi (2015)
Duck, pork, turkey, and rabbit meat	Spain	Collado, Guarro, and Figueras (2009)
Ducks (cloaca swabs fecal samples)	Costa Rica	Bogantes et al. (2015)
Geese (cloaca swabs fecal samples)	Costa Rica	Bogantes et al. (2015)
Cattle (fecal samples)	Iran	Aski, Tabatabaei, Khoshbakht, and Raeisi (2016)
Cattle (fecal samples)	England	Merga et al. (2013)
Cattle (fecal samples)	Italy	Giacometti et al. (2015a)
Sheep (fecal samples)	Iran	Aski et al. (2016)
Feacal samples from pigs, chicken, turkey, cattle, sheep, and duck	India	Sekhar, Tumati, Chinnam, Kothapalli, and Sharif (2017)
Fecal swab samples of chicken, ducks, cattle, and pigs	India	Sekhar et al. (2018)
Imported and locally processed beef	Malaysia	Shah et al. (2012a)
Beef, lamb, and pork	Australia	Rivas et al. (2004)
Pork, beef, and chicken	Poland	Zacharow et al. (2015a)
Farmed caimans (fecal samples)	Brazil	Oliveira et al. (2017)
Raw milk	UK	Scullion et al. (2006)
Raw milk and retail raw beef	Malaysia	Shah et al. (2012b)
Raw milk	Turkey	Ertas et al. (2010)
Raw milk	Italy	Caruso et al. (2019)
Cow and buffalo milk	Turkey	Yesilmen et al. (2014)
Water buffalo milk	Italy	Serraino et al. (2013a)
Raw milk	Italy	Parisi et al. (2019)
Cow and water buffalo raw milk	Italy	Giacometti et al. (2015a)
Raw milk	Brazil	Pianta, Thompsen Passos, Hepp, and de Oliveira (2007)
Raw milk from vending machines	Italy	Traversa et al. (2019)
Raw milk	Brazil	Cruzado-Bravo et al. (2020)
Raw milk	Italy	Caruso et al. (2020)
Raw milk	Spain	Nieva-Echevarria et al. (2013)
Raw cow and buffalo milk	Italy	De Cesare et al. (2016); Giacometti et al. (2013b)
Minas frescal cheese	Brazil	Cruzado-Bravo et al. (2020)
Fresh village cheese	Turkey	Yesilmen et al. (2014)

(Continues)

TABLE 3 (Continued)

Habitat/source	Country	Reference
Ricotta cheese	Italy	De Cesare et al. (2016)
Ricotta cheese, mozzarella cheese, and conditioning liquid	Italy	Giacometti et al. (2013a)
Ricotta cheese	Italy	Giacometti et al. (2013b)
Sheep ricotta cheese	Italy	Scarano et al. (2014)
Mozzarella cheese and ricotta cheese	Italy	Serraino and Giacometti (2014)

TABLE 4 Excerpt of studies on the occurrence of *A. butzleri* in fish and seafoods

Habitat/source	Country	Reference
Fish and shellfish	India	Rathlavath et al. (2017b)
Finfish and shellfish	India	Laishram et al. (2016)
Fresh fish	India	Rathlavath, Mishra, Kumar, and Nayak (2016)
Fresh fish meat	Portugal	Vicente-Martins et al. (2018)
Mytilus galloprovincialis	Italy	Bonerba et al. (2015)
Mussels, razor clams, clams, shrimps, squids and octopuses	Germany	Zhang, Alter, and Gölz (2019)
Shellfish	Italy	Mottola et al. (2016b)
Mussels, clams, and cockles	Spain	Morejón, González, and Ferrús (2017)
Fish and shellfish	India	Rathlavath, Kumar, and Nayak (2017a)
Japanese giant abalone, *Haliotis gigantea*	Japan	Mizutani et al. (2019)
Clams, mussels, oysters, razor clams, scallops and surf clam	Chile	Collado et al. (2014)
Shellfish	Spain	Nieva-Echevarria et al. (2013
Bivalve molluscs	Italy	Leoni et al. (2017)

4 | *A. BUTZLERI* PATHOGENICITY

A. butzleri, together with *A. cryaerophilus*, *A. skirrowii*, and *A. thereius*, are considered human pathogens, and recent progress and outcomes on their pathogenicity made *A. butzleri* and *A. cryaerophilus* to be included in the list of microbes considered a serious hazard to human health by the International Commission on Microbiological Specifications for Foods (2002).

In particular, *A. butzleri* has been associated with severe diarrhea, enteritis, and bacteremia in humans (Table 5). *A. butzleri* causes a more long-lasting and aqueous, but less bloody and acute diarrhea than the taxonomically related *Campylobacter jejuni* (Karadas et al., 2016). Possible routes of transmissions in humans can be oro-fecal, sewage-, water-, or food-borne, directly from animals and from person-to-person (Collado et al., 2010; Ferreira, Queiroz, Oleastro, & Domingues, 2016; González, Suski, & Ferrús, 2010; Jacob, Loir, & Feuerpfeil, 1993; Jacob, Woodward, Fuerpfeil, & Johnson, 1998; Lee & Choi, 2013; Merga, Royden, Pandey, & Williams, 2014; Shah, Saleha, Zunita, & Murugaiyah, 2011; Vandamme et al., 1992a). The possible severity and protraction of the symptoms might require an antibiotic treatment that can be complicated by the (multiple) antibiotic resistance of the strains of this species (Fanelli et al., 2020). Recently, Jiménez-Guerra, Moreno-Torres, Moldovan, Navarro-Marí, and Gutiérrez-Fernández (2020) reported a case of *A. butzleri* intestinal colonization in an elderly patient with immunodeficiency and other concomitant diseases. This condition was diagnosed during routine analyses including the screening for multidrug-resistant microorganisms' colonization on selective growth media. Although the patient showed no signs or symptoms of infectious enteritis and received no antibiotic therapy, the authors underlined that there is no sufficient knowledge on human colonization caused by this microorganism that is fundamental to understand the clinical approach to be taken in cases like this. Moreover, it is possible that this pathogen may cause extraintestinal illnesses. In 2013, there was the first description of an *Arcobacter* peritonitis in an elderly peritoneal dialysis (PD) patient with renal failure and a PD catheter (Yap, Kwan, To, & Chan, 2013). Even if the authors were not able to provide a diagnosis at the species level, they reported that the usual prophylactic antibiotic protocol was ineffective to prevent the onset of the *Arcobacter* infection.

Regarding the animal sources, *A. butzleri* has been isolated from aborted fetuses and placentas of bovine, porcine, and ovine origin (de Oliveira, Baetz, Wesley, & Harmon, 1997; Vandamme et al., 1992b; Wesley, Baetz, & Larson, 1996), from diarrheic non-human primates such as macaques

TABLE 5 Diseases caused by *A. butzleri* in humans

Disease	Underlying conditions	Reference
Bacteremia	Chronic lymphocytic leukemia	Arguello, Otto, Mead, and Babady (2015)
	Liver cirrhosis	Yan et al. (2000)
Bacteremia	Acute gangrenous appendicitis	Lau, Woo, Teng, Leung, and Yuen (2002)
Bacteremia	The mother of the neonate had a prenatal bleeding	On, Stacey, and Smyth (1995)
Diarrhea, abdominal cramps	Diabetes mellitus I hyperuricemia, alcohol abuse	Lerner, Brumberger, and Preac-Mursic (1994)
Outbreak of recurrent abdominal cramps	Ten otherwise healthy children	Vandamme et al. (1992a)
Outbreak of diarrheal and nondiarrheal illnesses	Not specified for the 51 diarrhoic- and the 12 nondiarrhoic- patients	Lappi et al. (2013)
Chronic diarrhea	Not specified	Fernàndez, Krause, and Villanueva (2004)
Nausea, abdominal pain with cramps, and acute diarrhea	Not specified	Kayman et al. (2012)
Gastroenteritis	Not specified	Burnens, Schaad, and Nicolet (1992)
Travelers' diarrhea	Not specified	Jiang et al. (2010)
Infection/diarrhea/abdominal pain	10 of 61 had underlying disease: four were HIV seropositive, and three were immunocompromised (postrenal graft, celiac disease, and chemotherapy for cerebellar astrocytoma). One had dementia, one had insulin-dependent diabetes mellitus and one had hepatitis C	Vandenberg et al. (2004)
(bloody) Diarrhea/vomiting/ abdominal pain	Not specified	Ferreira, Júlio, Queiroz, Domingues, and Oleastro (2014a)
Gastrointestinal complaints/diarrhea	Not specified	Samie et al. (2007)
Enteritis in 46 patients of which 19 had acute gastroenteritis, 30 had coexisting medical conditions and eight had chronic colitis	Not specified	Van den Abeele, Vogelaers, Van Hende, and Houf (2014)
Diarrhea (892/1,596 diarrheic stool samples)	Not specified	Webb et al. (2016)
Diarrhea and/or abdominal pain, bloody stools, vomiting and/or fever	Not specified	Prouzet-Mauléon, Labadi, Bouges, Ménard, and Mégraud (2006)
Intestinal colonization with no signs or symptoms	Arterial hypertension, hypercholesterolemia, osteoporosis, Sjögren syndrome, and rosacea	Jiménez-Guerra et al. (2020)

(Anderson, Kiehlbauch, Anderson, McClure, & Wachsmuth, 1993; Higgins, Messier, Daignault, & Lorange, 1999) as well as from diarrheic pigs, cattle, horses, ostriches, and tortoises (Ho, Lipman, & Gaastra, 2006; Kiehlbauch et al., 1991; Vandamme et al., 1992b).

Since 1992, when Vandamme et al. (1992b) stated "although the association with diarrheal illness in humans and animals is striking, the clinical significance of *A. butzleri* remains to be proven," advancements have been done regarding the pathogenicity of this bacterium, even if the overall pathomechanisms of *A. butzleri* disease are not fully understood to date. Bücker, Troeger, Kleer, Fromm, and Schulzke (2009) elucidated the mechanism underlying the diarrhea caused by *A. butzleri* using as model the human colonic carcinoma cells (HT-29/B6). These authors showed that *A. butzleri* may induce an impairment of the epithelial barrier function of the intestine, which, in turn, is caused by changes in tight junction proteins and induction of epithelial apoptosis, all mechanisms that are consistent with a leak flux type of diarrhea in *A. butzleri* infection (Bücker et al., 2009). In addition, several studies have been carried out to characterize *A. butzleri* adhesion, invasion, and cytotoxicity to host

TABLE 6 *In vitro* studies on the pathogenicity of *A. butzleri*

Cell line	Sample origin	Adhesion (number of positive samples/number of tested samples)	Invasion (number of positive samples/number of tested samples)	Cytotoxicity (number of positive samples/number of tested samples)	References
Hep-2	Sea water	6/17	ND	ND	Carbone et al. (2003)
	Human stool	12/12	4/12	3/12	Vandenberg et al. (2004)
Hep-2	Zooplankton	4/4	ND	ND	Gugliandolo, Irrera, Lentini, and Maugeri (2008)
	Human (feces)	3/3	ND	ND	Fernàndez, Flores, and Inzunza (2010)
	Animal (mussels and feces from pelican, bovine, duck, dog, sparrow)	33/33	ND	ND	Fernàndez et al. (2010)
	River water	15/15	ND	ND	Fernàndez et al. (2010)
	Meat (chicken giblets and carcass)	21/21	ND	ND	Fernàndez et al. (2010)
	River water/animal (chicken liver for human consumption)	4/4	ND	ND	Fernández et al. (2013)
Hela	Sea water	6/17	ND	ND	Carbone et al. (2003)
	River water	1/8	0/8	ND	Musmanno, Russi, Lior, and Figura (1997)
	Animal and human	ND	ND	3/3	Johnson and Murano (2002)
	River water/Human (diarrhea)/animal (cattle and poultry)	ND	ND	7/7	Johnson and Murano (2002)
	Zooplankton	4/4	ND	ND	Gugliandolo et al. (2008)
INT407	River water	1/8	0/8	ND	Musmanno et al. (1997)
	River water/human (diarrhea)/animal (cattle and poultry)	ND	ND	6/6	Johnson and Murano (2002)
Vero	River water	ND	ND	17/18	Musmanno et al. (1997)
	Sea water	ND	ND	5/17	Carbone et al. (2003)
	Meat (pork, chicken, beef)	ND	ND	76/80	Villarruel-Lopez et al. (2003)
	Zooplankton	ND	ND	3/4	Gugliandolo et al. (2008)
CHO	River water	ND	ND	17/18	Musmanno et al. (1997)
Caco-2	Human (blood)	1/1	0/1	ND	Ho et al. (2007)

(Continues)

TABLE 6 (Continued)

Cell line	Sample origin	Adhesion (number of positive samples/number of tested samples)	Invasion (number of positive samples/number of tested samples)	Cytotoxicity (number of positive samples/number of tested samples)	References
	Meat (turkey, duck, pig, chicken, and beef)	6/6	6/6	ND	Levican, Alkeskas, Gunter, Forsythe, and Figueras (2013)
	Animal (clams, mussels)	4/4	3/4	ND	Levican et al. (2013
	Sewage	2/2	2/2	ND	Levican et al. (2013)
	Human	3/3	3/3	ND	Karadas et al. (2013)
	Meat (chicken)	3/3	3/3	ND	Karadas et al. (2013)
	Human (stools)/animal (poultry)/poultry slaughterhouse	6/6	6/6	ND	Ferreira et al. (2014c)
IPI-2I	Human (blood)	1/1	0/1	ND	Ho et al. (2007)
HT-29	Human	2/3	1/3	ND	Karadas et al. (2013)
	Meat (chicken)	2/3	2/3	ND	Karadas et al. (2013)
HT-29/B6	Human (feces)/meat (chicken)	5/6	5/6	4/6	Karadas et al. (2016)
	Human (feces)	ND	ND	24/24	Brückner et al. (2020)
IPEC-J2	Human (feces)/meat (chicken)	4/6	2/6	0/6	Karadas et al. (2016)

Caco-2, human colorectal adenocarcinoma cell line; CHO, Chinese hamster ovary cell line; HeLa, human cervix carcinoma cell line; Hep-2, human cervix carcinoma cell line (HeLa contamination); INT407, HeLa derivative; HT-29/HT-29/B6, human colorectal adenocarcinoma cell line; IPEC-J2, porcine jejunal epithelial cell line; IPI-2I, porcine intestinal epithelioid cell line; Vero, kidney epithelial cell line.
ND, not determined.

cells. As shown in Table 6, adherence and cytotoxicity are most recurrently detected effects. Recently, novel insight into the pathophysiology of the *A. butzleri* infection was provided by Zur Bruegge et al. (2014) who investigated the impact of *A. butzleri* on human macrophages, demonstrating that this pathogen induces a proinflammatory response in THP-1 derived macrophages and has limited ability for intracellular survival. Strain-specific invasion and survival capabilities as well as variations in motility were found in the *A. butzleri* used in this study, allowing to hypothesize that this strain-specific variations may be responsible for the clinical differences, ranging from asymptomatic to severe, observed in animals and human patients infected with this pathogen (Zur Bruegge et al., 2014). Moreover Ferreira, Queiroz, Oleastro, and Domingues (2014c) reported that six *A. butzleri* strains had weak hemolytic activity against human erythrocytes and Wilson, Otth, Aron, and Fernández (2010) found 10 *A. butzleri* strains, isolated from animal and river water sources, to be high-susceptible to human blood serum, probably also due to the bactericidal action of the complement. In this perspective, the underlying pathomechanisms and patient clinical conditions (e.g. immunodeficiency) of the reported bacteremia cases (Table 5) need to be better understood. Ferreira et al. (2014c) investigated the pathogenic effect of *A. butzleri* on Caco-2 human intestinal epithelial cell line. They reported the ability to adhere to and invade the Caco-2 cells, albeit with strain-related differences, in accordance to the previous studies using the same cell line (Ferreira et al., 2014c). A pre-existing inflammation of the intestinal cells seemed not to increase the adhesion and invasion abilities for the most tested strains, and the authors pointed out that these two latter mechanisms underlie the possibility for colonization and persistence or dissemination to other tissues (Ferreira et al., 2014c). For the first time, they reported the intracellular survival ability of some *A. butzleri* strains in Caco-2 cells but subsequent replication was not observed. Karadas et al. (2016) studied

the pathogenetic potential of *A. butzleri* in two different cell lines: HT-29/B6 (human colon adenocarcinoma cell line) and IPEC-J2 (porcine jejunal cell line). The six tested *A. butzleri* strains showed strain-related adhesion and invasion abilities that, anyway, were observed mainly in the human cell line (the authors suggested that the mucus layer produced by HT-29/B6 cells could positively affect the *A. butzleri* adhesiveness and invasiveness) then in the porcine one, while the *A. butzleri* cytotoxic effect was observed only in the human cell line. In addition to the previous findings by Bücker et al. (2009), Karadas et al. (2016) reported that also nonadhesive and noninvasive *A. butzleri* strains can induce epithelial barrier impairment in HT-29/B6 monolayers and, to a lesser extent, also in IPEC-J2 monolayers leading to wonder if these differences could rely on differences between the two cell lines or on differences between the two host species. More recently, Brückner, Fiebiger, Ignatius, and Golz (2020) reported that cytotoxic effects on the HT-29/B6 cell line were also caused by 24 *A. butzleri* isolates they tested that were isolated from human stool samples. The authors classified the great majority of them as "high or "moderate" cytotoxic isolates (just one isolates was identified with low cytotoxic ability), being similar to *A. lanthieri* isolates, and different from *A. cryaerophilus* isolates that seems to have low cytotoxic effects, even if for the latter two species more studies testing a large number of isolates are needed (Brückner et al., 2020). Since the cytolethal distending toxin (CDT) related genes (*cdt*ABC) have not been found in *A. butzleri* (Brückner et al., 2020), other mechanisms might be investigated to understand the *A. butzleri* cytotoxicity. Additionally, despite the reported strain-related differences regarding the *A. butzleri* pathogenetic potential, Fernández, Flores, Villanueva, Medina, and Carrizo (2013) reported that four *A. butzleri* strains previously classified as weakly adherent to HEp-2 cells could progressively enhance their adherence ability to the same cells after serial intraperitoneal passages in Rockefeller (3 to 6 weeks age) mice.

Several animal studies have been conducted on *A. butzleri* pathogenicity. Oral infection of caesarean-derived 1-day-old piglets with *A. butzleri* strains (isolated from human feces and swine) allowed their multiplication in the gut and their invasion into internal organs of infected animals (Wesley et al., 1996). Experimental oral infection of 3- and 5-day-old chickens and turkeys, with strains of different origins resulted in host-dependent invasive capacity and virulence of the *A. butzleri* strains (Wesley & Baetz, 1999). The effects of *A. butzleri* infection on albino rats employing bacterial strains isolated from stools or caecal content of healthy chickens or pigs have been studied (Adesiji, 2010; Adesiji et al., 2012; Adesiji, Emikpe, & Olaitan, 2009; Adesiji, Emikpe, & Opalekunde, 2011). After oral infection with 1×10^9 colony forming unit (cfu), several histopathological lesions were reported, such as liver necrosis, desquamation, and necrosis of the small intestine with villous erosion (Adesiji et al., 2009). Moreover reduced activity and appetite, loss of weight, rough fur, high rectal temperature and mucous, nonbloody, self-limiting diarrhea (it ceased after 3 weeks with no antibiotic therapy) were observed after oral infection with 1×10^2 to 1×10^9 cfu, and *A. butzleri* fecal shedding was observed along 5 weeks with a peak within 3 weeks (Adesiji, 2010). In addition, oral administration of 1×10^3 to 1×10^9 cfu resulted in serum electrolyte alterations and in packed cell volume, platelets, neutrophils, and lymphocytes increasing, that were related to the infection dose and the sampling time (Adesiji et al., 2012). The injection of 1×10^8 *A. butzleri* cfu in the albino rats' proximal ductus deferens caused testicle degeneration and sperm count and motility decrease, but an improvement of the clinical signs without antibiotic therapy was observed after ca. 20 days postinfection (Adesiji et al., 2011). Medina, Flores-Martin, Fonseca, Otth, and Fernandez (2014), and Medina et al. (2019) elucidated the mechanisms associated with phagocytosis of *A. butzleri* by *Acanthamoeba castellanii*, a free-living amoeba widely found in environmental matrices such as soil and water, to which the emerging pathogen may establish endosymbiotic relationships, and analyzed the transcriptional pattern of *A. butzleri* flagellar and some putative virulence-related genes during the interaction with this host. The histopathological and immunohistochemical changes after peroral (PO), intraperitoneal (IP), and intramammary (IMG) administration of 1×10^9 cfu of *A. butzleri* strain isolated from a patient with gastrointestinal infection, were investigated in BALB/c mice by Ata and Çakir (2016). Diarrhea, weakness, low body temperature, and tremors were common findings, while conjunctivitis was observed in mice infected by IMG administration. The clinical signs and subsequent mortality were most widespread in IP and IMG groups. Lesions involved serosal vessels, mainly in the large intestine, and mesenterial lymph nodes (PO group); furthermore, hepatomegaly, splenomegaly (IP group), mammary gland swelling, exudation, and abscess (IMG group) were observed. Acute or chronic inflammations and necrosis or congestions were found in several organs (IP group). Pyogranulomatosis, necrotizing inflammation, and interstitial fibrosis were pathological findings in mammary gland and in adjacent subcutaneous tissues (IMG group), while *A. butzleri* was reisolated from several organs until 5 days postinfection (Ata & Çakir, 2016).

Açik, Yüksel, Ulucan, and Çetinkaya (2016) investigated the pathogenicity and histopathology of *A. butzleri* using zebrafish as model organism. The resulting mean infective dose (ID50) of *A. butzleri* was 1.3×10^8 cfu/mL and 1×10^5 cfu/mL by immersion and intraperitoneal injection, respectively. During the experimental period of 21 days, Açik et al. (2016) did not observe any clinical sign or gross lesion of disease in the zebrafish groups infected (by immersion and intraperitoneal routes) with the ID50 of *A. butzleri*. Liver,

kidney, spleen, gaster and other visceral organs revealed an acute inflammation characterized by neutrophil and plasma cells and local necrosis or congestion (Açik et al., 2016). Moreover, peritonitis, leukocyte infiltration, villous atrophy and septicemia were observed (Açik et al., 2016), whereas no gross and microscopic lesions were observed in the healthy noninfected zebrafishes (controls) tested.

All these findings confirm the enteropathogenicity of *A. butzleri* providing detailed information on the adhesive, invasive, and cytotoxic properties of this pathogen but recall for *in vivo* studies on the underlying immunopathological mechanisms of infection. In the last decade, such studies have been undertaken, revealing that *A. butzleri* induces intestinal, extraintestinal, and systemic immune responses in gnotobiotic (i.e., secondary abiotic) IL-$10^{-/-}$ mice (Gölz et al., 2015a; Heimesaat et al., 2015a), engendering changes in the expression of genes involved in tissue degradation and in proinflammatory and regulatory immune responses (Heimesaat, Alter, Bereswill, & Gölz, 2016). Such immune responses were highly dependent on Toll-like-receptor-4, that is the main receptor for lipooligosaccharide and lipopolysaccharide (LPS) of Gram-negative bacteria (Gölz et al., 2015b; Gölz, Alter, Bereswill, & Heimesaat, 2016a; Heimesaat et al., 2015b). Moreover, Gölz, Alter, Bereswill, and Heimesaat (2016b) demonstrated that, upon infection of gnotobiotic IL-$10^{-/-}$ mice, *A. butzleri* induces less distinct proinflammatory sequelae than *Campylobacter jejuni*, but more pronounced intestinal and systemic immune responses than commensal *Escherichia coli* in a strain-dependent manner, highlighting the immunopathogenic potential of this pathogen in vertebrate hosts.

5 | VIRULENCE DETERMINANTS

Since the first genomic sequences of *A. butzleri* (*Ab*) published by Miller et al. (2007), 42 assemblies have been deposited in NCBI portal so far. The availability of these data has enabled the identification and distribution of virulence-associated genes (VAGs), which confers this genus an important genetic endowment for host invasion and colonization (Ferreira et al., 2016).

The genomic sequence of *A. butzleri* RM4018 revealed the presence of several homologues of *Campylobacter jejuni* virulence determinants, including the fibronectin-binding protein *cad*F and *cj*1349, the invasion protein *cia*B, the virulence factor *mvi*N, the phospholipase *pld*A, and the *tly*A hemolysin. In addition, *A. butzleri* RM4018 also harbors: *irg*A, homologue of the iron-regulated outer membrane protein in *Vibrio cholerae* (Goldberg, DiRita, & Calderwood, 1990), which was associated with pathogenicity of urinary tract by *E. coli* (Johnson et al., 2005); *hec*A, a member of the hemagglutinin family, *hec*B, which encodes a related hemolysin activation protein; and *Iro*E, an enterobactin hydrolase present in uropathogenic *E. coli*. Moreover, Rovetto et al., 2017 identified a genetic locus comprising *waa*F and *waa*C, which were described as virulence determinants in *A. thereius*, but also in *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumonia*, and other *Campylobacteraceae* (Delucia et al., 2011; Nilsson, Prathapam, Grove, Lapointe, & Six, 2018; Oldfield, Moran, Millar, Prendergast, & Ketley, 2002). This cluster, which has a slightly different organization and content from *A. thereius* (Rovetto et al., 2017), was identified as similar also in *A. butzleri* 55, *A. butzleri* 34_O, and *A. butzleri* 39_O, while *A. butzleri* 6V and *A. butzleri* ED-1 have genes unlikely arranged and the cluster contains several glycosyltransferases with no orthologues in the other *A. butzleri* strains (Fanelli et al., 2019, 2020).

Through a comparative analysis among five *A. butzleri* genomic sequences, Fanelli et al. (2019, 2020) identified additional VAGs, some of which are shared by all strains, such as the transcriptional regulator *vir*F, while other are uniquely present in one, as occurred for the gene coding for virulence associated protein VirE, which was present only in one *A. butzleri* strain.

A. butzleri is a motile bacterium by means of one single polar flagellum, which is recognized as a virulence trait. The bacterial flagellar motor is comprised by a core structure (inner membrane stator complexes MotA4B2 and the C-ring), a dedicated type III secretion system (T3SS) export apparatus, the inner membrane MS-ring and the P- and L-rings. Although conserved across bacterial genera, in *A. butzleri* these core components present an intermediate (Chaban, Coleman, & Beeby, 2018) motor structure, missing the motor accessory proteins FlgP, FlgQ, FlgT, which harbors the homologue FlgO, an outer membrane protein required for flagellar motility in *Vibrio cholerae*, highly conserved in *Vibrio* spp. (Zhu et al., 2017). According to the analysis performed by Isidro et al. (2020) there are 34 genes coding for flagellar proteins, which are clustered into two genomic loci of 20 and eight genes, while *fla*A and *fla*B, *mot*A and *mot*B are located outside the cluster.

In addition to the known virulence determinants, by analyzing 49 genomic sequences of *A. butzleri* isolated from different sources Isidro et al. (2020) reported additional elements suggested to be involved in the pathogenicity of this species. Among these, Isidro et al. (2020) retrieved in 25 strains the urease cluster *ure*D(AB)CEFG, which in *H. pylori* is associated with host infection (Gupta, Maurya, Verma, & Verma, 2019), as well as homologues of the quorum sensing S-ribosylhomocysteine lyase *lux*S (Plummer, 2012), the serine protease *htr*A (Boehm, Lind, Backert, & Tegtmeyer, 2015), the invasion associated gene *iam*A and the ferric uptake regulator *fur*, recognized virulence factors in *Campylobacter* spp. (Bolton, 2015).

The occurrence of virulence determinants from different sources has been usually determined evaluating the presence of the virulence genes recognized in the genome of *A. butzleri* ATCC 49616 (Miller et al., 2007). Douidah et al. (2012) developed a PCR-assay to detect nine VAGs validating this method over 319 human and animal *Arcobacter* strains, and all these genes were retrieved in 182 *A. butzleri* isolates. Whiteduck-Léveillée et al. (2016) developed a multiplex PCR assay to target eight VAGs in *Arcobacter* spp., and among 100 tested strains of *A. butzleri* from various human and animal fecal sources the *cia*B (89%) and *mvi*N (81%) were detected more frequently than the *tly*A (66%), *pld*A (58%), *cj1349* (20%), *hec*B (14%), and each of the *irg*A and *hec*A (9%).

Tabatabaei, Aski, Shayegh, and Khoshbakht (2014) reported the presence of six virulence genes (*cad*F, *cia*B, *cj*1349, *mvi*N, *pld*A, and *tly*A) in 100% of the 113 *A. butzleri* strains isolated in Southern Iran from various sources. These data were conflicting with those of Collado, Jara, Vásquez, and Telsaint (2014) who reported lower prevalence of these genes in *A. butzleri* from shellfish.

Rathlavath et al. (2017b) isolated 147 *A. butlzeri* from seafood and coastal environment in India and recorded different occurrence of VAG among isolates, with the following rates: *mvi*N (100%), *cj1349* (97.2%), *cia*B (95.9%), *tly*A (91.8%), *pld*A (91.1%), and *cad*F (89.7%), while lower detection rates were observed for *hec*A (10.8%), *hec*B (19%), *iro*E (12.9%), and *irg*A (17.6%).

Zacharow, Bystroń, Wałecka-Zacharska, Podkowik, and Bania (2015a) evaluated the prevalence of VAGs in *A. butzleri* isolates from pork, beef, and chicken meat in Poland. All isolates harbored the *tly*A gene, and most of them carried *cia*B, *mvi*N, *pld*A, *cad*F, and *cj*1349 genes, with *cia*B occurring with a higher frequency in poultry as compared with pork and *irg*A more frequent in poultry than in beef.

Parisi et al. (2019) evaluated, by whole genome sequencing (WGS) analysis, the presence of VAGs in 10 *A. butzleri* isolated from milk, reporting that all strains carried *cad*F, *pld*A, *cia*B, *cj*1349, *mvi*N, and *tly*A virulence factors genes, six strains harbored *iro*E, five *irg*A, and one *hec*B.

Recently, Medina et al. (2019) performed a transcriptional analysis by RT-PCR of flagellar and putative virulence genes of *A. butzleri* as an endocytobiont of *Acanthamoeba castellanii*. The authors reported a biphasic transcriptional pattern: an upregulation of *cia*B, *cad*F, *pld*A, and *mvi*N genes as well as flagellar genes (*fla*A, *fla*b, *flg*H, *mot*A) was detected before *A. butzleri* became established as an endocytobiont of *A. castellanii*, whereas a significant and sustained decrease in the expression of these genes occurred after *A. butzleri* was established as an endocytobiont. This adaptive response appeared necessary for the transition from extracellular to intraamoebic vacuolar environment, thus enabling the intraamoebic survival of *A. butzleri* as an endocytobiont (Medina et al., 2019).

In conclusion, the availability of an increasing number of *A. butzleri* genomic sequences is widening the list of putative VAGs in this species, whose occurrence appeared to be differently distributed among isolates form different sources and geographic distribution, although further studies are needed to recognize additional genes and demonstrate their role in virulence. The *in silico* analysis might also favor the development of detection assays targeting a wider range of VAGs, that can improve epidemiological studies, providing an updated landscape of this underestimated enteropathogenic bacterium.

6 | ANTIBIOTIC AND HEAVY METAL RESISTANCE

To date, no reference protocols and standard interpretive criteria are available for antimicrobial susceptibility testing (AST) of *A. butzleri*, hampering an univocal and comparable evaluation of antimicrobial susceptibility for this bacterium (Fanelli et al., 2019; Ferreira et al., 2016). In recent years, a first attempt to overcome this drawback was made by Riesenberg et al. (2017), who proposed a protocol for AST of *A. butzleri* by the broth microdilution method. Regardless of this, several authors in the last few years, reported the susceptibility of *A. butzleri*, isolated from various sources, towards several antibiotics (Tables 7 and 8), mainly using the disk diffusion method and referring to Clinical and Laboratory Standards Institute (CLSI) Interpretive Standards for *Enterobacteriaceae* and for *Campylobacter* spp. Among the more frequently tested antibiotics (Table 7), *A. butzleri* showed high frequency of susceptibility towards the hydrophilic fluoroquinolone ciprofloxacin, tetracyclines, and aminoglycosides such as gentamicin, kanamycin, and streptomycin. For this reason, these classes of antibiotics are reported by some authors for treatment of *Arcobacter* infections (Collado et al., 2014; Ferreira et al., 2016; Rahimi, 2014; Rathlavath et al., 2017b; Vandenberg et al., 2006). But as concerns tetracyclines, high percentages of resistant *A. butzleri* isolates/strains were recently reported by Yesilmen, Vural, Erkan, and Yildirim (2014) and Vicente-Martins, Oleastro, Domingues, and Ferreira (2018), who found that 100% (10/10 *A. butzleri* isolates) and 95.4% (62/65 *A. butzleri* strains) were resistant towards this antibiotic, respectively (Table 7). Also for ciprofloxacin quite high percentages of resistant *A. butzleri* are being reported. Ferreira et al. (2013), Dekker et al. (2019), and Isidro et al. (2020) found that 55.8% (24/43 *A. butzleri* isolates), 47% (25/53 *A. butzleri* isolates), and 40.9% (9/22 *A. butzleri* strains) of the tested *A. butzleri* isolates were resistant towards this antibiotic, respectively (Table 7). Similar differences in frequency of resistant *A. butzleri* are reported for erythromycin (macrolide) (ranging from 0% to 100%), nalidixic acid (hydrophobic quinolone) (ranging from 21.9%

TABLE 7 Prevalence of *A. butzleri* susceptibility towards frequently tested antibiotics (reported in more than five studies)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics											Method	Interpretive criteria	References
		Amp	Cef	Chl	Cip	Ery	Gen	Kan	NA	Str	Tet	Van			
96 (beef, pork, and chicken meat from retail shops)	Japan	0.0% (0/96) R		30.2% (29/96) R		0.0% (0/96) R		0.0% (0/96) R	63.5% (61/96) R	0.0% (0/96) R	0.0% (0/96) R	100% (96/96) R	Disk diffusion	Not reported[a]	Kabeya et al. (2004)
9 (stool samples of patients with gastroenteritis)	Turkey	100% (9/9) R			100% (9/9) S	100% (9/9) S	100% (9/9) S		77.8% (7/9) S; 22.2% (2/9) R		55.6% (5/9) S; 44.4% (4/9) IR		E-test strips	CLSI, 2006 for *Campylobacter* spp.; CLSI 2010 for *Enterobacteriaceae*	Kayman et al. (2012)
43 (poultry and poultry slaughterhouse)	Portugal	97.7% (42/43) R		2.3% (1/43) R	55.8% (24/43) R		0.0% (0/43) R					100% (43/43) R	Broth micodilution	CDC, 2006, 2010; CLSI, 2005	Ferreira et al. (2013)
48 (dairy plant)	Portugal	56.2% (27/48) R	97.9% (47/48) R		2.1% (1/48) R	0.0% (0/48) R	0.0% (0/48) R		100% (48/48) R				Agar dilution	EUCAST, 2017 for *Campylobacter* spp.; CLSI, 2015 for *Enterobacteriaceae*	Ferreira et al. (2017)
62 (edible bivalve molluscs)	Chile	45.2% (28/62) R			3.2% (2/62) R	0.0% (0/62) R	0.0% (0/62) R		83.9% (52/62) R				Agar dilution	CLSI, 2008, 2009, 2011 for *Campylobacter* spp.	Collado et al. (2014)
64 (poultry meat)	Iran	57.8% (37/64) R		9.4% (6/64) R	1.6% (1/64) R	1.6% (1/64) R	0% (0/64) R	0% (0/64) R	21.9% (14/64) R	0% (0/64) R	0% (0/64) R	98.4% (63/64) R	Disk diffusion	CLSI, 2006	Rahimi (2014)

(Continues)

TABLE 7 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics											Method	Interpretive criteria	References
		Amp	Cef	Chl	Cip	Ery	Gen	Kan	NA	Str	Tet	Van			
10 (cow milk, water buffalo milk, and fresh village cheese)	Turkey	100.0% (10/10) R				80.0% (8/10) R; 20% (2/10) IR			40.0% (4/10) R; 10% (1/10) IR; 50% (5/10) S	30.0% (3/10) R; 70/% (7/10) S	100.0% (10/10) R	90.0% (9/10) R; 10% (1/10) IR	Disk diffusion	CLSI, 2002 (bacteria isolated from animals); CLSI 2010 for *Enterobacteriaceae*	Yesilmen et al. (2014)
79 (pork, beef, chicken meat)	Poland	85% (67/79) R	66% (52/79) R		28% (22/79) R	62% (49/79) R	20% (16/79) R				21% (17/79) R		Disk diffusion	CLSI, 2010 for *Enterobacteriaceae*	Zacharow et al. (2015b)
22 (cattle and sheep fecal samples)	Iran	86.4% (19/22) R		40.9% (9/22) R	0.0% (0/22) R	0.0% (0/22) R	4.5% (1/22) R	0.0% (0/22) R	50% (11/22) R		0.0% (0/22) R	100% (22/22) R	Disk diffusion	CLSI, 2006, 2010 for *Campylobacter* spp. and *Enterobacteriaceae*	Aski et al. (2016)
63 (stool samples of patients with gastrointestinal illness)	Belgium	90.5% (57/63) R			12.7% (8/63) R	23.8% (15/63) R	0% (0/63) R				14.3% (9/63) R		E-test strips	EUCAST, 2015 for *C. coli, Enterobacteriaceae* and nonspecies related breakpoints	Van den Abeele, Vogelaers, Vanleare, and Houf (2016)
23 (broiler meat, minced beef meat, cattle slaughterhouse swabs, and wastewater)	Turkey	100% (23/23) R			NS	100% (23/23) R	NS		100% (23/23) R		NS		Disk diffusion	CLSI, 2015	Elmali and Can (2017)

(Continues)

TABLE 7 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics											Method	Interpretive criteria	References
		Amp	Cef	Chl	Cip	Ery	Gen	Kan	NA	Str	Tet	Van			
17 (fresh vegetables)	Spain				11.76% (2/17) R								Disk diffusion, E-test strips	CLSI, 2010 for *Campylobacter* spp.	González et al. (2017)
147 (81 from fish, 40 from shellfish, 26 from coastal water	Not reporte	72.1% (106/14 R; 13.6% (20/147 IR; 14.2% (21/147 S	99.3% (146/14 R; 0.68% (1/147) IR;	3.4% (5/147) R; 23.8% (35/147 IR; 72.7% (107/14 S	1.36% (2/147) R; 10.2% (15/147 IR; 88.4% (130/14 S	30.6% (45/147 IR; 69.3% (102/14 S	100% (147/14 S	100% (147/14 S	70.7% (104/14 R; 15.6% (23/147 IR; 13.6% (20/147 S	100% (147/14 S	100% (147/14 S	100% (147/14 R	Disk diffusion	CLSI, 2015	Rathlavath et al. (2017b)
75 (beef, dairy milk, cattle and cattle farm environment)	Not reported	74.7% (56/75) R	36% (27/75) R		17.3% (13/75) R	30.7% (23/75) R	12% (9/75) R				6.7% (5/75) R		Disk diffusion, E-test strips[b]	CLSI, 2002; CLSI, 2010 for *Enterobacteriaceae*	Shah et al. (2017)
80 (poultry meat, water sources and human enteritis cases)	Czech Republic	86.3% (69/80) R; 13.8% (11/80) S		62.5% (50/80) R; 17.5% (14/80) IR; 20.0% (16/80) S	1.3% (1/80) R; 98.8% (79/80) S	22.5% (18/80) IR; 77.5% (62/80) S	2.5% (2/80) R; 97.5% (78/80) S		88.8% (71/80) R; 5.0% (4/80) IR; 6.3% (5/80) S	1.3% (1/80) R; 98.8% (79/80) S	1.3% (1/80) R; 18.8% (15/80) IR; 80.0% (64/80) S		Disk diffusion	CLSI, 2015 for *Campylobacter* spp., other *Enterobacteriaceae* and other bacteria	Šilha et al. (2017)

(Continues)

TABLE 7 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics											Method	Interpretive criteria	References
		Amp	Cef	Chl	Cip	Ery	Gen	Kan	NA	Str	Tet	Van			
16 (animals, foods of animal origin and humans)	India			81.3% (13/16) R	0% (0/16) R	50.0% (8/16) R	18.7% (3/16) R	31.2% (5/16) R	37.5% (6/16) R		0% (0/16) R	100.0% (16/16) R	Disk diffusion	CLSI, 2014	Soma, Srinivasa, Bindu, Subramanyam, and Mohammad (2017)
65 (ready-to-eat packaged vegetables, poultry, pork, beef, fish)	Portugal	47.6% (31/65) R	98.5% (64/65) R	87.7% (57/65) R	27.7% (18/65) R	10.8% (7/65) R	0% (0/65) R		100% (65/65) R		95.4% (62/65) R		Agar dilution	EUCAST, 2017 for *C. jejuni* and *C. coli;* CLSI, 2015 for *Enterobacteriaceae*	Vicente-Martins et al. (2018)
53 (fresh local and frozen imported chicken meat)	Ghana				47% (25/53) R								Disk diffusion	absence of inhibition zone to classify isolates as R	Dekker et al. (2019)
3 (*A. butzleri* LMG 10828 and two strains from shellfish)	Italy	100% (3/3) R	100% (3/3) R	33.3% (1/3) R; 66.7% (2/3) IR	100% (3/3) S	66.7% (2/3) R; 33.3% (1/3) IR	100% (3/3) S	100% (3/3) S	33.3% (1/3) R; 66.7% (2/3) IR	100% (3/3) S	66.7% (2/3) R; 33.3% (1/3) IR	100% (3/3) R	Disk diffusion; broth microdilution	CLSI, 2015 for *Enterobacteriaceae* and *Staphylococcus* spp.	Fanelli et al. (2019)
3 (A. butzleri LMG 10828 and two strains from pre-cut ready to eat vegetables)	Italy	100% (3/3) R	100% (3/3) R	66.7% (2/3) R; 33.3% (1/3) IR	100% (3/3) S	33.3% (1/3) R; 66.7% (2/3) IR	100% (3/3) S	100% (3/3) S	100% (3/3) IR	100% (3/3) S	100% (3/3) IR	100% (3/3) R	Disk diffusion; broth microdilution	CLSI, 2015 for *Enterobacteriaceae* and *Staphylococcus* spp.	Fanelli et al. (2020)

(Continues)

TABLE 7 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics											Method	Interpretive criteria	References
		Amp	Cef	Chl	Cip	Ery	Gen	Kan	NA	Str	Tet	Van			
22 (slaughterhouse environments and poultry samples, meat and vegetables from retail markets, raw milk and dairy plant environment, river water, human diarrhea)	Portugal/France	45.5% (10/22) R; 9.1% (2/22) IR[c]; 45.5% (10/22) S	95.5% (21/22) R; 4.5% (1/22) S		40.9% (9/22) R; 59.1% (13/22) S	18.2% (4/22) R; 81.8% (18/22) S	100% (22/22) S		100% (22/22) R				Agar dilution	CDC, 2018 for *Campylobacter coli*; CLSI, 2016 for *Enterobacteriaceae*	Isidro et al. (2020)

Amp: ampicillin; Cef: cefotaxime; Chl: chloramphenicol; Cip: ciprofloxacin; Ery: erythromycin; Gen: gentamicin; Kan: kanamycin; NA: nalidixic acid; Str: streptomycin; Tet: tetracycline; Van: vancomycin.

R: resistant; S: susceptible; IR: intermediate resistant.

CLSI: Clinical & Laboratory Standards Institute; CDC: Centers for Disease Control and Prevention; EUCAST: European Committee on Antimicrobial Susceptibility Testing.

NS: not specified because *A. butzleri* antimicrobial susceptibility results are reported along with those obtained for other *Arcobacter* spp. isolates.

[a]Kabeya et al. (2004) reported the breakpoints for each antibiotic they used but they did not report the relevant reference.

[b]Only number and percentage of *A. butzleri* isolates resulted as resistant in both tests are reported.

[c]In Isidro et al. (2020) reported as "borderline resistant phenotype."

TABLE 8 Prevalence of *A. butzleri* susceptibility towards not frequently tested antibiotics (reported in one to five studies)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics													Method	Interpretive criteria	References
		Amo	Amo + CA	Azi	Cefp	Ceft	Cep	Cli	Clo	Lev	Met	Pip	Su + tri	Tri			
96 (beef, pork and chicken meat from retail shops)	Japan						94.8% (91/96) R				96.9% (93/96) R		68.8% (66/96) R		Disk diffusion	Not reported[a]	Kabeya et al. (2004)
43 (poultry and poultry slaughter-house)	Portugal	97.7% (42/43) R			97.7% (42/43) R							97.7% (42/43) R		100% (43/43) R	Broth micodi-lution	CDC, 2006, 2010; CLSI, 2005	Ferreira et al. (2013)
48 (dairy plant)	Portugal									2.1% (1/48) R					Agar dilution	EUCAST, 2017 for *Campylobacter* spp.; CLSI, 2015 for *Enterobacte-riaceae*	Ferreira et al. (2017)
62 (edible bivalve molluscs)	Chile									3.2% (2/62) R					Agar dilution	CLSI, 2008, 2009, 2011 for *Campylobacter* spp.	Collado et al. (2014)
64 (poultry meat)	Iran			95.3% (61/64) R			100% (64/64) R	75.0% (48/64) R			93.8% (60/64) R				Disk diffu-sion	CLSI, 2006	Rahimi (2014)
10 (cow milk, water buffalo milk, and fresh village cheese)	Turkey	80.0% (8/10) R; 20% (2/10) S	60.0% (6/10) R; 40% (4/10) S		100.0% (10/10) R	40.0% (4/10) R; 60% (6/10) S			100.0% (10/10) R						Disk diffu-sion	CLSI, 2002 (bacteria isolated from animals); CLSI 2010 for *Enterobacteri-aceae*	Yesilmen et al. (2014)

(Continues)

TABLE 8 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics													Method	Interpretive criteria	References
		Amo	Amo + CA	Azi	Cefp	Ceft	Cep	Cli	Clo	Lev	Met	Pip	Su + tri	Tri			
79 (pork, beef, chicken meat)	Poland		63% (50/79) R												Disk diffusion	CLSI, 2010 for *Enterobacteriaceae*	Zacharow et al. (2015b)
22 (cattle and sheep fecal samples)	Iran						100% (22/22) R	90.9% (20/22) R						100% (22/22) R	Disk diffusion	CLSI, 2006, 2010 for *Campylobacter* spp. and *Enterobacteriaceae*	Aski et al. (2016)
23 (broiler meat, minced beef meat, cattle slaughterhouse swabs and wastewater)	Turkey			NS											Disk diffusion	CLSI, 2015	Elmali and Can (2017)
17 (fresh vegetables)	Spain									11.76% (2/17) R					Disk diffusion, E-test strips	CLSI, 2010 for *Campylobacter* spp.	Gonzàlez et al. (2017)
147 (81 from fish, 40 from shellfish, 26 from coastal water	Not reported		41.4% (61/147) R; 23.1% (34/147) IR; 35.3% (52/147) S				100% (147/147) R								Disk diffusion	CLSI, 2015	Rathlavath et al. (2017b)

(Continues)

TABLE 8 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics												Method	Interpretive criteria	References
		Amo	Amo + CA	Azi	Cefp	Ceft	Cep	Cli	Clo	Lev	Met	Pip	Su + tri	Tri			
80 (poultry meat, water sources, and human enteritis cases)	Czech Republic		33.8% (27/80) R; 11.3% (9/80) IR; 55% (44/80) S				77.5% (62/80) R; 1.3% (1/80) IR; 21.3% (17/80) S	97.5% (78/80) R; 2.5% (2/80) S							Disk diffusion	CLSI, 2015 for *Campylobacter* spp., other *Enterobacteriaceae* and other bacteria	Šilha et al. (2017)
65 (ready-to-eat packaged vegetables, poultry, pork, beef, fish)	Portugal									23.1% (15/65) R					Agar dilution	EUCAST, 2017 for *C. jejuni* and *C. coli;* CLSI, 2015 for *Enterobacteriaceae*	Vicente-Martins et al. (2018)
22 (slaughterhouse environments and poultry samples, meat and vegetables from retail markets, raw milk and dairy plant environment, river water, human diarrhea)	Portugal/France									40.9% (9/22) R; 0% (0/22) IR[b]; 59.1% (13/22) S					Agar dilution	CDC, 2018 for *Campylobacter coli*; CLSI, 2016 for *Enterobacteriaceae*	Isidro et al. (2020)

(Continues)

TABLE 8 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics												Method	Interpretive criteria	References
		Ami	Cefz	Ceftr	Dox	Enro	Ge + Amo	Nor	Oxy	PG	P+N	Rif	Spi			
10 (cow milk, water buffalo milk, and fresh village cheese)	Turkey				50.0% (5/10) R; 10% (1/10) IR; 40% (4/10) S	30.0% (3/10) R; 10% (1/10) IR; 60% (6/10) S	30.0% (3/10) R; 70% (7/10) S			100.0% (10/10) R	80.0% (8/10) R; 20% (2/10) IR		40.0% (4/10) R; 60% (6/10) S	Disk diffusion	CLSI, 2002 (bacteria isolated from animals); CLSI 2010 for *Enterobacteriaceae*	Yesilmen et al. (2014)
79 (pork, beef, chicken meat)	Poland							30% (24/79) R						Disk diffusion	CLSI, 2010 for *Enterobacteriaceae*	Zacharow et al. (2015b)
22 (cattle and sheep fecal samples)	Iran	4.5% (1/22) R	95.5% (21/22) R	100% (22/22) R		4.5% (1/22) R			0.0% (0/22) R			100% (22/22) R		Disk diffusion	CLSI, 2006, 2010 for *Campylobacter* spp. and *Enterobacteriaceae*	Aski et al. (2016)
63 (stool samples of patients with gastrointestinal illness)	Belgium				36.5% (23/63) R									E-test strips	EUCAST, 2015 for *C. coli, Enterobacteriaceae* and nonspecies-related breakpoints	Van den Abeele et al. (2016)
23 (broiler meat, minced beef meat, cattle slaughterhouse swabs and wastewater)	Turkey											100% (23/23) R		Disk diffusion	CLSI, 2015	Elmali and Can (2017)

(Continues)

TABLE 8 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics												Method	Interpretive criteria	References
		Ami	Cefz	Ceftr	Dox	Enro	Ge + Amo	Nor	Oxy	PG	P+N	Rif	Spi			
147 (81 from fish, 40 from shellfish, 26 from coastal water)	Not reported							2.04% (3/147) IR; 97.9% (144/147) S						Disk diffusion	CLSI, 2015	Rathlavath et al. (2017b)
80 (poultry meat, water sources and human enteritis cases)	Czech Republic	100% (80/80) S			5.0% (4/80) R; 22.5% (18/80) IR; 72.5% (58/80) S	6.3% (5/80) R; 30.0% (24/80) IR; 63.8% (51/80) S				100.0% (80/80) R				Disk diffusion	CLSI, 2015 for *Campylobacter* spp., other *Enterobacteriaceae* and other bacteria	Šilha et al. (2017)
3 (*A. butzleri* LMG 10828 and two strains from shellfish)	Italy									100% (3/3) R				Disk diffusion; broth microdilution	CLSI, 2015 for *Enterobacteriaceae* and *Staphylococcus* spp.	Fanelli et al. (2019)
3 (*A. butzleri* LMG 10828 and two strains from pre-cut ready to eat vegetables)	Italy									100% (3/3) R				Disk diffusion; broth microdilution	CLSI, 2015 for *Enterobacteriaceae* and *Staphylococcus* spp.	Fanelli et al. (2020)

(Continues)

TABLE 8 (Continued)

Tested *A. butzleri* isolates/strains (source of isolation)	Country	Antibiotics												Method	Interpretive criteria	References
		Azt	Cefx	Cefta	Col	Cot	Ert	Imi	Mero	Oxa	PB	Sul	Tob			
23 (broiler meat, minced beef meat, cattle slaughterhouse swabs and wastewater)	Turkey							NS						Disk diffusion	CLSI, 2015	Elmali and Can (2017)
147 (81 from fish, 40 from shellfish, 26 from coastal water)	Not reported		100% (147/147) R	87.7% (129/147) R; 7.5% (11/147) IR; 4.7% (7/147) S	2.7% (4/147) R; 97.2 % (143/147) S		41.4% (61/147) R; 12.9% (19/147) IR; 45.5% (67/147) S	100% (147/147) S	19% (28/147) R; 6.1% (9/147) IR; 74.8% (110/147) S		100 % (147/147) S	100% (147/147) R		Disk diffusion	CLSI, 2015	Rathlavath et al. (2017b)
80 (poultry meat, water sources and human enteritis cases)	Czech Republic	95.0% (76/80) R; 2.5% (2/80) IR; 2.5% (2/80) S								100.0% (80/80) R			100.0% (80/80) S	Disk diffusion	CLSI, 2015 for *Campylobacter* spp., other *Enterobacteriaceae* and other bacteria	Šilha et al. (2017)
16 (animals, foods of animal origin and humans)	India		37.5% (6/16) R			93.7% (15/16) R								disk diffusion	CLSI, 2014	Soma et al. (2017)

Amo: amoxicillin, Amo + CA: amoxicillin + clavulanic acid, Azi: azithromycin, Cefp: cefoperazone, Ceft: ceftiofur, Cep: cephalothin, Cli: clindamycin, Clo: cloxacillin, Lev: levofloxacin, Met: methicillin, Pip: piperaciclin, Su + Tri: sulfamethoxazole + trimethroprim, Tri: trimethoprim, Ami: amikacin, Cefz: cefazolin, Ceftr: ceftriaxone, Dox: doxycycline, Enro: enrofloxacin, Ge + Amo: gentamicin + amoxicillin, Nor: norfloxacin, Oxy: oxytetracycline, PG: penicillin G, P + N: penicillin + novobiocin, Rif: rifampicin, Spi: spiramycin, Azt: aztreonam, Cefx: cefoxitin, Cefta: ceftazidime, Col: colistin, Cot: co-trimoxazole, Ert: ertapenem, Imi: imipenem, Mero: meropenem, Oxa: oxacillin, PB: polymyxin B, Sul: sulphamethizole, Tob: tobramycin.

CLSI: Clinical & Laboratory Standards Institute; CDC: Centers for Disease Control and Prevention; EUCAST: European Committee on Antimicrobial Susceptibility Testing.

R: resistant; S: susceptible; IR: intermediate resistant.

NS: not specified because *A. butzleri* antimicrobial susceptibility results are reported along with those obtained for other *Arcobacter* spp. isolates.

[a] Kabeya et al. (2004) reported the breakpoints for each antibiotic they used but they did not report the relevant reference.

[b] In Isidro et al. (2020) reported as "borderline resistant phenotype."

to 100%), and chloramphenicol (phenicol) (ranging from 2.3% to 87.7%) (Table 7). Otth, Wilson, Cancino, and Fernández (2004), referring to chloramphenicol, suggested that such differences could be due to local differences in the usage of this antibiotic. In fact, it is reported that the large use of antibiotics in farm animals affects the prevalence of antibiotic resistant bacteria in them and, in a certain extent, in humans (Tang et al., 2017). *A. butzleri* showed high frequency of resistance towards ampicillin and cefotaxime (β-lactam antibiotics) and the glycopeptide vancomycin (Table 7). The latter resistance could be ascribed to the intrinsic resistance of Gram-negative bacteria towards glycopeptides, molecules with high molecular weight (1450 to 1500 Da) that could not pass through porins of the outer membrane to reach the cell wall that represents their site of action (Fanelli et al., 2019; Nicolosi, Scalia, Nicolosi, & Pignatello, 2010). Beyond this, genetic determinants of antibiotic resistance were described for *A. butzleri*. Isidro et al. (2020) performed a comparative genomic study on 49 *A. butzleri* strains and, in order to explore the repertoire of antibiotic resistance–related genes, they exploited Comprehensive Antibiotic Resistance Database (CARD) and Resfinder database. In addition to three β-lactamase encoding genes (*bla*1-*bla*3), one chloramphenicol acetyltransferase encoding gene (*cat*) (putatively related to β-lactams and chloramphenicol resistance, respectively) and one gene putatively encoding for an antibiotic resistance protein, they found a large repertoire of genes that were related to 19 efflux pump (EP1–EP19) systems, 10 of which were present in all the analyzed *A. butzleri* genomes, and genes related to a putative type I secretion system (T1SS). On the basis of these findings, it seems that the extrusion mechanisms play a pivotal role in the antibiotic resistance of this microorganism. The same authors found in *A. butzleri* strains, reported as phenotypically resistant to erythromycin, a predicted truncated TetR regulator protein (due to single-nucleotide polymorphism or small indels or the presence of insertion sequence element) in EP16. Isidro et al. (2020) hypothesized that this mutation leads to the overexpression of EP16 and consequently to an increase of erythromycin extrusion, representing the first description of an erythromycin-resistance genetic determinant in *A. butzleri*. Moreover, they found in *A. butzleri* strains phenotypically resistant to ciprofloxacin and levofloxacin fluoroquinolones, the Thr-85-Ile substitution in the quinolone-resistance determining region of GyrA as previously described by Abdelbaqi et al. (2007a). Also Fanelli et al. (2019, 2020), performing a genomic characterization of four *A. butzleri* strains isolated from shellfish and precut ready-to-eat vegetables, found several genes putatively related to antibiotic resistance. *A. butzleri* antibiotic resistance genes were predicted by BLASTP search querying the Antibiotic Resistance genes Database (ARDB), beta lactamase database, CARD database and searching keywords within UniProtID entry list obtained by functional annotation. They found, in addition to β-lactamase encoding genes (*bla*, *bla*2, *hcp*C, and one putative metallo β-lactamase encoding gene), chloramphenicol acetyltransferase encoding genes (*cat*3, *wbp*D), efflux-pump and transporter protein related genes (*acr*B, *arp*C, *bep*D, *bep*E, *mdt*B, *mdt*E, *mex*A, *mex*B, and *tol*C encoding for multidrug efflux pump components; *mac*A and *mac*B encoding for macrolide export proteins; *fsr* encoding for a fosmidomycin resistance protein; *tet*A encoding for a tetracycline resistance protein and *bcr* encoding for a bicyclomycin resistance protein), other antibiotic-resistance genes not coding for efflux pumps or transporters such as those related to polymyxin resistance (*arn*A, *arn*B, *ept*A), methicillin resistance (*hlp*A), mupirocine resistance (*ile*S), ciprofloxacin and ampicillin resistance (*rel*E), ribosome targeting antibiotic resistance (*rlm*N), streptothricin resistance (*stt*H) and bacitracin resistance (*upp*P).

Although to date standard criteria for classification of multidrug-resistant (MDR) *A. butzleri* have not been established, some authors classified *A. butzleri* strains as MDR because they showed resistance towards at least three (in addition to penicillin and oxacillin resistance) (Šilha, Pejchalová, & Šilhová, 2017) or four (Shah et al., 2017; Zacharow, Bystroń, Wałecka-Zacharska, Podkowik, & Bania, 2015b) antibiotics. Fanelli et al. (2020), based on the MDR definition proposed by Magiorakos et al. (2012), classified all the five *A. butzleri* strains they tested as MDR according to the criteria proposed for *Enterobacteriaceae* and for *Staphylococcus aureus*.

A. butzleri antibiotic-resistance represents therefore a matter of concern, and, in this perspective, Sousa, Luís, Oleastro, Domingues, and Ferreira (2019) investigated the possibility to use polyphenols as resistance modulators in *A. butzleri*. They found that stilbenes, such as resveratrol and pinosylvin, reduced *A. butzleri* resistance towards some antibiotics probably acting as efflux pump inhibitors.

A correlation between antibiotic and heavy metal resistance might exist in bacteria, as observed, for example, in *Salmonella* Typhimurium (Yu, Gunn, Wall, & Fanning, 2017), *Listeria monocytogenes* (Mata, Baquero, & Perez-Diaz, 2000), *Pseudomonas aeruginosa* (Caille, Rossier, & Perron, 2007), and *Burkholderia cepacia* (Hayashi, Abe, Kimoto, Furukawa, & Nakazawa, 2000), but in *A. butzleri* it has been few investigated. The onset of bacterial resistance towards heavy metals could be explained by selective pressure exerted on bacteria by these compounds, which have accumulated in several environments principally due to anthropic activities (Xavier et al., 2019). As reviewed by Baker-Austin, Wright, Stepanauskas, and McArthur (2006) and Yu et al. (2017), the coselection of antibiotic and heavy metal resistance, although not fully understood, may be explained by coresistance. This can happen when genes related to antibiotic

and heavy metal resistance are located on the same mobile genetic element (e.g. conjugative plasmids and transposons) and can be easily horizontally transferred together. Cross-resistance may also contribute when not molecule-specific mechanisms give rise to resistance towards both antibiotics and heavy metals (such as those represented by multidrug efflux pumps). Coregulation is another factor that intervenes when the same regulatory system affects both mechanisms related to antibiotic and heavy metal resistance. Also biofilm production is involved, not only because biofilm would hinder the diffusion of antimicrobials, such as antibiotics and heavy metals, to bacterial cells or because horizontal genetic transfer can easily occur within biofilm, but because it would represent a complex environment in which additional mechanism would be involved in bacterial antimicrobial resistance. In recent years, Otth, Solís, Wilson, and Fernández (2005) and Fanelli et al. (2020) investigated the *A. butzleri* susceptibility to heavy metals by the agar dilution method and considered resistant, since no reference protocols are available, *A. butzleri* isolates for which the heavy metal minimal inhibitory concentration (MIC) was >1 mM. Otth et al. (2005) found that 50 *A. butzleri* isolated from chicken liver, mussels, river water, and stools of bovines, ducks and pelicans were all susceptible towards mercury, silver and chromate salts while were all resistant towards nickel, lead, iron, manganese, molybdenum, and cobalt salts. Similarly, Fanelli et al. (2020) found that also the *A. butzleri* strains they tested (two strains isolated from shellfish, two from precut ready-to-eat vegetables and the *A. butzleri* type strain LMG 10828^{T}) were susceptible to chromate and resistant towards molybdate and cobalt salts. Moreover, they found that these strains were susceptible to cadmium and resistant to zinc and copper salts. Fanelli et al. (2019, 2020), analyzing the genomes of the *A. butzleri* strains they sequenced, found several genes putatively related to heavy metal resistance. The great majority of them were genes related to efflux pump systems or coding for transport proteins, putatively conferring resistance to arsenic (*ars*B), mercury (*mer*T), zinc (*znt*B), copper (*cop*A, *cop*Z), or towards various combinations of two or more heavy metals, such as cobalt, zinc, cadmium, silver, copper, nickel. and magnesium (*cor*C, *rcn*A, *cad*A, *czc*B, *czc*D, cation efflux system- and Resistance-nodulation-division (RND) efflux pump-related genes). Moreover, genes not coding for transport or efflux pump proteins were found, including genes encoding an arsenate reductase (*ars*C) putatively related to arsenic resistance, a metal-sensitive transcriptional repressor (*cso*R) involved in the cellular response to increasing concentrations of copper (Liu et al., 2007) and a sensor kinase (*cus*S) that was found to be important in copper tolerance (Outten, Huffman, Hale, & O'Halloran, 2001).

7 | ISOLATION, IDENTIFICATION, AND TYPING

A. butzleri is difficult to isolate in a comprehensive manner (Collado & Figueras, 2011; Merga et al., 2011). Culture conditions must therefore be sensitive, that is able to detect even minimum number of isolates of this species, inclusive, that is general enough to allow growth of all strains of this species, and specific, that is selective enough to inhibit non-target growth of other organisms that may be present in complex matrices also containing a background microflora such as (fermented) foods. No standard microbiological method for the enumeration, isolation, or detection of *A. butzleri* in different matrices is to date available, although many combinations of growth conditions, culturing techniques, and antimicrobial agents have been proposed (Table 9). In general, the protocol for the isolation of *A. butzleri* includes a selective enrichment step of 48 hr in a broth containing antibiotics, followed by the filtration of the broth through a 0.45 μm filter over an agar medium containing or not antibiotics, which is incubated for 48 to 72 hr.

Comprehensive molecular methods to detect *A. butzleri* in complex matrices such as foods, feces, or water samples do not exist, although a number of novel and modified primer sets that target universal genes for multiplex and/or quantitative polymerase chain reaction (PCR) have been proposed (Abdelbaqi et al., 2007b; Brightwell et al., 2007; De Boer et al., 2013; Douidah, De Zutter, Vandamme, & Houf, 2010; Harmon, & Wesley, 1997; Houf, Tutenel, De Zutter, Van Hoof, & Vandamme, 2000; Kabeya, Kobayashi, Maruyama, & Mikami, 2003; Pentimalli, Pegels, García, Martín, & González, 2009). A PCR hybridization strategy using degenerate primers to amplify *gly*A fragments directly from samples, thereafter subjected to species-specific oligodeoxyribonucleotide probe hybridizations, to identify and distinguish between *Campylobacter jejuni*, *C. coli*, *C. lari*, *C. upsaliensis*, *A. butzleri*, and an *A. butzleri*-like species was developed by Al Rashid et al. (2000), whereas Petersen, Harrington, Kortegaard, and On (2007) developed a seminested PCR to allow sensitive detection of all *Epsilonbacteria*, including *A. butzleri*, with species separation undertaken by denaturing gradient gel electrophoresis (DGGE). *A. butzleri* has been also detected by using DNA microarrays (Quiñones, Parker, Janda, Miller, & Mandrell, 2007), rybotyping (Kiehlbauch, Plikaytis, Swaminathan, Cameron, & Wachsmuth, 1991), fluorescent *in situ* hybridization (FISH) (Fera et al., 2010), amplified fragment length polymorphism (AFLP) (On, Harrington, & Atabay, 2003), by loop-mediated isothermal amplification (LAMP) (Wang, Seo, Lee, & Choi, 2014), and by Matrix-associated laser desorption/ionization-time of flight

TABLE 9 Methods for the microbiological isolation of *A. butzleri*

Enrichment (AMA[a])	Solid medium (technique)[b]	Solid medium (AMA)	Atmosphere[c]	Temperature (°C)	Reference
Arcobacter media	*Arcobacter* media (dp)	5-fu, amp-B, cfp, nvb, tmp	Microaerobic	28	Mandisodza, Burrows, and Nulsen (2012)
Arcobacter media	*Arcobacter* media (dp)	Amp-B, cfp, tcp	Aerobic	30	Fera et al. (2010)
Arcobacter media (5-fu, amp-B, cfp, chx, nvb, tmp)	*Arcobacter* media (dp)	5-fu, amp-B, cfp, chx, nvb, tmp	Microaerobic	28	Van Driessche et al. (2004)
Brucella (cfp, chx pip, tmp)	Brain-heart infusion	Cefsulodin, irgasan, nvb	Aerobic	25	Morita et al. (2004)
Brucella (cfp, chx pip, tmp)	Mueller-Hinton (dp)	Chx, cfp, pip, tmp	Aerobic	24	De Boer, Tilburg, Woodward, Lior, and Johnson (1996)
Brucella (cfp, chx pip, tmp)	Mueller-Hinton (dp)	Chx, cfp, pip, tmp	Aerobic	25	Morita et al. (2004)
CAT (amp-B, cfp, tcp)	Blood agar (mf)	Amp-B, cfp, tcp	Microaerobic	30	Ho et al. (2008)
CAT (amp-B, cfp, tcp)	Blood agar (mf), mCCDA (dp)	None	Aerobic	37	Atabay and Corry (1998)
CAT (amp-B, cfp, tcp)	CAT (dp)	Amp-B, cfp, tcp	Aerobic	37	Atabay and Corry (1998)
CAT (amp-B, cfp, tcp)	Karmali (dp)	None	Aerobic	25, 30	Atabay and Corry (1998)
None	CAT (dp)	Amp-B, cfp, tcp	Aerobic	37	Atabay and Corry (1998)
None	Blood agar (mf), mCCDA (dp)	None	Aerobic	37	Atabay and Corry (1998)
None	*Arcobacter* media (dp)	5-fu, amp-B, cfp, chx, nvb, tmp	Microaerobic	28	Van Driessche et al. (2004)
None	*Arcobacter* media (dp)	Amp-B, cfp, tcp	Aerobic	30	Fera et al. (2010)

[a] AMAs are 5-fluorouracil (5-fu), amphotericin B (amp-B), cefoperazone (cfp), cyclohexamide (chx), novobiocin (nvb), piperacillin (pip), teicoplanin (tcp), and trimethoprim (tmp).

[b] Plating techniques used were direct plating (dp) or membrane filtration (mf).

[c] Incubation of *A. butzleri* cultures occurred at ambient oxygen conditions (aerobic) or at reduced oxygen conditions (microaerobic) consisting of 5 to 6% O_2, 6 to 10% CO_2, 0 to 7% H_2, and 79 to 85% N_2.

(MALDI-TOF) mass spectrometry (Alispahic et al., 2010). Moreover, several restriction fragment length polymorphism analysis (RFLP) of different PCR-amplified fragments, that is of the *16S rRNA* (Cardarelli-Leite et al., 1996; Figueras, Collado, & Guarro, 2008), *23S rRNA* (González, Moreno, González, Hernández, & Ferrús, 2006; Hurtado & Owen, 1997), and *gro*EL (Kärenlampi, Tolvanen, & Hänninen, 2004) genes have been able to detect *A. butzleri*.

Several methods are available to type *A. butzleri*. These mainly include: restriction endonuclease analysis by pulsed field gel electrophoresis (REA-PFGE) (Hume et al., 2001), enterobacterial repetitive intergenic consensus polymerase chain reaction (ERIC-PCR) (Vandamme et al., 1993), randomly amplified polymorphic DNA PCR (RAPD-PCR) (Houf, De Zutter, Van Hoof, & Vandamme, 2002), AFLP (On, Atabay, Amisu, Coker, & Harrington, 2004) and MLST (Miller et al., 2009). Among these, MLST is more informative and unambiguous, easy to carry out also semiautomatically, by automating labor-intensive pipetting steps and DNA sequencing. Moreover, in MLST the data analysis is easier as it analyzes sequence data and allelic profiles rather than fingerprints, that can be shared throughout the online platform (http://pubmlst.org/arcobacter).

Another reliable and reproducible technique, based on sequence data analysis, is WGS, which is able to resolve even a single base change between genomes (Fusco & Quero, 2014) and is finding increasing use in the epidemiologic analysis of bacterial pathogens (Schürch, Arredondo-Alonso, Willems, & Goering, 2018).

8 | *A. BUTZLERI* SURVIVAL ALONG THE FOOD-CHAIN AND MITIGATION STRATEGIES

Several studies have investigated the ability of *A. butzleri* to survive in conditions mimicking those encountered along the food chain and several measures have been developed and tested to control and prevent the survival and growth of this emerging pathogen.

A. butzleri has been found to grow at temperatures ranging from 15 to 39 °C, whereas it does not grow at 40 °C (Hilton, Mackey, Hargreaves, & Forsythe, 2001). By contrast, one *A. butzleri* isolated from a patient with liver cirrhosis resulted to grow at 42 °C (Yan et al., 2000) and certain human isolates of this species were found to grow in Ellin-ghausen McCullough Johnson Harris (EMJH) medium at 10 °C by D'Sa and Harrison (2005). The viability of *A. butzleri* cells in stationary phase has been found to decrease during storage at 4 °C, whereas two log decrease was observed for it after 24 hr of freezing at −20 °C (Hilton et al., 2001). For these reasons, Hilton et al. (2001) suggested that *A. butzleri* survives better in chilling than in freezing conditions. Šilha, Morávková, Škodová, and Vytřasová (2019) investigated the survival of two *A. butzleri* strains at different processing temperatures finding that they survived 7 days at −18 °C, 7 and 14 days at 5 °C, 77 and 189 days at both 15 and at 25 °C, and 7 and 35 days at 37 °C, while intermediate or high biofilm-forming activity was observed at all tested temperatures, but a semiquantitative approach was used and range of classification was not clarified. Moreover, these authors found that 51, 52.5, and 54.25 °C (mean values) were lethal temperatures for both *A. butzleri* strains in distilled water, physiological saline and brain heart infusion (BHI) broth, respectively (Šilha et al., 2019). *A. butzleri* growth can be completely inhibited at a pH 5 at 5 °C and at a pH 9 at 5 °C in the presence of 8% NaCl (Park & Ha, 2015). Weak organic acids, such as citric and acetic acids, inhibit the growth of *A. butzleri* after 4 to 5 hr of incubation at 30 °C (Cervenka, Malíková, Zachová, & Vytrasová, 2004). Antimicrobial activity against *A. butzleri* has been demonstrated for sea buckthorn (*Hippophae rhamnoides* L.) extracts (Kučerová, Šilha, Vytřasová, & Švecová, 2017) cold pressed terpeneless Valencia orange oil (Nannapaneni et al., 2009), bergamot, citral, and linalool (Fisher et al., 2007), as well as for cinnamaldehyde (with a MIC of 32 μg/mL), thymol providing 80 and 51% inhibition with MIC_{50} and $MIC_{25,}$ respectively, carvacrol (with MICs ranging from 64 to 128 μg/mL), caffeic acid and tannic acid (with MICs ranging from 64 to 128 μg/mL), and eugenol (with MICs ranging from 128 to 256 μg/mL) (Cervenka, Peskova, Pejchalova, & Vytrasova, 2008). *A. butzleri* is inhibited by rosemary, bay, cinnamon, and clove (Irkin, Abay, & Aydin, 2011). Moreover, it is inactivated in 10, 15.0, and 10 to 15% in Incidur- and Desprej- and Guaa Profi Pool- disinfectant, respectively, whereas repeated passages of the strains in a medium with low concentration of disinfectant increases their primary resistance (Šilha et al., 2016).

Phillips (1999) examined the antimicrobial properties of preservatives at the concentrations usually found in foods and reported that 0.5, 1, and 2% lactic and citric acids inhibited growth in culture of *A. butzleri*, with citric acid being the more effective and yielding no viable cells after 8 hr. Sodium lactate (1/1.5/2%) inhibited growth up to only 7 to 8 hr, while sodium citrate (0.5/1/1.5%) was more effective than sodium lactate (Phillips, 1999). Nisin inhibited growth at 500 IU/mL over 5 hr. Moreover, it enhanced the effects of lactic and citric acids and sodium lactate but did not enhance the effect of sodium citrate (Phillips, 1999). Lately, Phillips and Duggan (2001) reported that EDTA (1 to 20 mM) alone, or in combination with nisin (500 IU/mL) or trisodium phosphate (0.5 mM) inhibited growth of *A. butzleri*, with short-term simultaneous exposure to the agents being more effective than sequential treatment.

Ferreira, Silva, Queiroz, Oleastro, and Domingues (2014b) investigated the effect of resveratrol on *A. butzleri*. Resveratrol presented MIC values of 100 μg/mL and, based on the time–kill curves, exhibited bactericidal activity, leading to a ≥3 log10 cfu/mL reduction of initial inoculums, for exponential phase cells incubated for 6 hr with 1 × MIC or with 2 × MIC after 24 hr for stationary phase cells. Such a reduction of the bactericidal effect of resveratrol on *A. butzleri* cells in the stationary phase with respect to that obtained on cells in exponential growth indicates that actively growing cells are more susceptible to resveratrol (Ferreira et al., 2014b). SEM analysis revealed disintegration of *A. butzleri* cells treated with resveratrol. Based on the time–kill curves, resveratrol exhibited a bacteriostatic or bactericidal activity that was dependent on the cellular growth phase and resveratrol concentration (Ferreira et al., 2014b). Duarte, Alves, Ferreira, Silva, and Domingues (2015) demonstrated that using resveratrol-hydroxypropyl-γ-cyclodextrin inclusion complexes (ICs) against *A. butzleri* improves resveratrol solubility. The ICs have anti-*Arcobacter* activity, inhibit biofilm formation, and promote the biofilm dispersion even at sub-MIC concentrations (Duarte et al., 2015). Bacterial resistance of *A. butzleri* may be due to efflux pumps whose genes have been found in the genomes of strains of this species (Fanelli et al., 2019; 2020; Isidro et al., 2020; Miller et al., 2007). Sousa et al. (2019) investigated the potential of polyphenols such as flavonoids, phenolic acids, and stilbenes, as efflux pump inhibitors evaluating their interaction with antibiotics, in order to enhance antibiotic activity against *A. butzleri*. They found that resveratrol and pinosylvin may act as resistance modulators since they can even revert antibiotic resistance (Sousa et al., 2019). However, all these features have been observed *in vitro* and in artificial substrates (broth and agar media).

A. butzleri has been demonstrated to survive in ultrahigh temperature, in pasteurized, and in raw cow's milk stored at 4 and 10 °C for 6 days (Giacometti et al., 2014) as well as during the production and storage at different temperatures (5, 10, and 20 °C) of water buffalo mozzarella cheese (Serraino et al., 2013b). Moreover, it survived in water buffalo and industrial ricotta cheese during storage at 6 °C for 5 days, whereas it grew during storage at 12 °C for 22 days (Giacometti et al., 2015b).

Kjeldgaard et al. (2009) investigated the survival and biofilm formation of *A. butzleri* strains under conditions mimicking those occurring in slaughterhouse environment using a chicken meat juice medium (CMJ). CMJ supported growth of *A. butzleri* at 15 and at 10 °C, whereas at 5 °C it enhanced the survival of this pathogen with respect to that achieved in brain heart infusion with less than a one log reduction after 77 days of incubation. Biofilms were produced by *A. butzleri* at temperatures ranging from 5 to 37 °C (Kjeldgaard et al., 2009).

On commercial vacuum packaged beef (beef with natural microflora) stored at −1.5 and 4 °C for 6 weeks only 0.3 and 1.3 log cfu cm^{-2} drops in numbers of *A. butzleri*, respectively, were registered (Balamurugan et al., 2013).

A. butzleri was found to possess a certain resistance (D_{10} = 0.27 kGy) to irradiation in vacuum-packaged ground pork, whereas an irradiation treatment of 1.5 kGy provided a 5 log reduction of *A. butzleri* cells (Collins et al., 1996). Storage at 5 °C combined with the presence of either 2% sodium lactate or 2% sodium lactate and 500 IU g^{-1} nisin or 1.5% sodium lactate and 1.5% sodium citrate was effective in controlling *A. butzleri* contamination in chicken (Long & Phillips, 2003), whereas the storage at 4 and at 10 °C of artificially contaminated chicken legs with different concentrations of *A. butzleri* (10^4 and 10^7 cfu/mL) allowed the growth of the strain (Badilla-Ramìrez et al., 2016). A significant reduction of *A. butzleri* cells was detected on chicken skin artificially inoculated with this pathogen and treated with IC_{50} <1 mg/mL of benzoic, caprylic, citric, lactic, lauric or malic acid, with the benzoic acid resulting in the most suitable for chicken skin decontamination based on the sensory analysis of cooked chicken (Skřivanová, Molatová, Matěnová, Houf, & Marounek, 2011).

Essential oil of rosemary (0.5% vol/wt) showed complete inhibitory activity against *A. butzleri* in cooked minced beef at 4 °C (Irkin et al., 2011).

9 | CONCLUSIONS

A. butzleri, recently emended to *Aliarcobacter butzleri* thanks to a taxogenomic approach, is an emerging pathogen for human and animals, whose main routes of transmission are fecally contaminated water and foods. Several studies have been recently carried out to unravel the mechanism of pathogenicity as well as the response of the immune system to this bacterium. Nevertheless, further studies are needed to demonstrate the enteropathogenicity of this microorganism in human and animals and the underling mechanisms. Advancements in this perspective have been made also thanks to the advent of genomics, which allowed to emend the taxonomy as well as to detect further virulence, antibiotic and heavy metal resistance determinants of this species, although their functionality should be still proven.

However, more genomes should be sequenced and more phenotypical characterizations of many strains isolated from different ecological niches should be performed to allow a deep comparative analysis that could bring to the light further phenotypic and genotypic traits as well the mechanisms

underlying the adaptation to the host/environment of this pathogen. Reference culture-based and culture-independent detection and typing methods should be defined and applied on a high number of samples to obtain prevalence data of this pathogen in various foods/animals allowing to detect reservoirs of this microorganism and obtain data on the exposure and infection dose. Although further studies on the specific food matrices rather than on the broth cultures should be carried out, *A. butzleri* is revealing resistance to various conditions including those encountered along the dairy and meat chains. However, further studies are needed to investigate the survival of *A. butzleri* to processing and storing conditions in the specific food matrices and understand the underlying mechanisms.

Moreover, as many other pathogens, *A. butzleri* is resistant to several antibiotics, thus calling the need of alternative therapies to control and prevent infections caused by this bacterium. Advances in this field are being made, but more studies aimed at investigating the role of different antimicrobials on artificially and naturally contaminated matrices/surfaces are needed.

Only by acquiring further knowledge, it will be feasible to assess and mitigate the risk posed by *A. butzleri* that will allow to predict, prevent, and control foodborne public health threats related to this pathogen.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

DC, FF, and VF wrote the manuscript. VF conceived the work, revised the overall manuscript, and was responsible of the overall review quality control. All authors contributed to the revision of the manuscript and read and approved the submitted manuscript.

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