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Field Interventions against Colonization of Broilers by *Campylobacter*

30

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32

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54 ABSTRACT: Poultry accounts for a high proportion of human campylobacteriosis cases, and the
55 problem of *Campylobacter* colonization of broiler flocks has proven to be intractable. Owing to their
56 broad host range and genetic instability, *Campylobacter* organisms are ubiquitous and adaptable in
57 the broiler farm environment, colonizing birds heavily and spreading rapidly after introduction into a
58 flock. This review examines strategies to prevent or suppress such colonization, with a heavy
59 emphasis on field investigations. Attempts to exclude *Campylobacter* via enhanced biosecurity and
60 hygiene measures have met with mixed success. Reasons for this are becoming better understood as
61 investigations focus on houses, ventilation, biosecurity practices, external operators, and compliance,
62 amongst other factors. It is evident that piecemeal approaches are likely to fail. Complementary
63 measures include feed and drinking water treatments applied in either preventive or suppressive
64 modes using agents including organic acids and their derivatives, also litter treatments, probiotics,
65 prebiotics, and alterations to diet. Some treatments aim to reduce the number of *Campylobacter*
66 organisms entering abattoirs by suppressing intestinal colonization just before slaughter; these
67 include acid water treatment or administration of bacteriophages or bacteriocins. Experimental
68 vaccines historically have had little success, but some recent subunit vaccines show promise.
69 Overall, there is wide variation in the control achieved, and consistency and harmonization of trials
70 is needed to enable robust evaluation. There is also some potential to breed for resistance to
71 *Campylobacter*. Good and consistent control of flock colonization by *Campylobacter* may require an
72 as-yet undetermined combination of excellent biosecurity plus complementary measures.

73

74 (Keywords: *Campylobacter*, broiler, intervention, farm, biosecurity, hygiene)

75

76	Nomenclature
77	C&D: cleaning and disinfection
78	cfu: colony-forming units
79	EFSA: European Food Standards Agency
80	EU: European Union
81	MCFA: medium-chain fatty acids
82	pfu: plaque-forming units
83	SCFA: short-chain fatty acids
84	UK: United Kingdom
85	

86 **Introduction**

87 Infection by thermophilic *Campylobacter* bacteria is currently the commonest zoonotic cause of
88 gastroenteritis among humans, in Europe and elsewhere (EFSA, 2014; FAO/WHO, 2009), with an
89 estimated eight- to 30-fold under-reporting of cases (Gölz et al., 2014). The species involved are
90 typically *Campylobacter jejuni* subsp. *jejuni* and *Campylobacter coli*, although *Campylobacter* species
91 *lari*, *upsaliensis*, and *helveticus* are also associated with diarrheal disease, more commonly in the
92 developing world (EFSA, 2011; On, 2001). Differences between *C. jejuni* and *C. coli* with respect to
93 virulence and of behavior in the food chain are unclear, although *C. jejuni* is the more common isolate
94 from broilers and from human disease cases.

95
96 Human disease is typically sporadic or occurs in small family-associated outbreaks. Outbreak and
97 case-control studies indicate that up to 30% of cases are attributable to consumption of chicken meat,
98 whilst subtyping studies suggest 50 to 80% of cases may be linked, directly or indirectly, to the bird
99 reservoir (EFSA, 2010c; van Rensberg et al., 2017). Recent retail surveys in the UK indicate that most
100 broiler carcasses at retail have some degree of *Campylobacter* contamination (FSA, 2018). The skin
101 of processed poultry, compared with that of pigs, appears particularly supportive of *Campylobacter*
102 survival (Gölz et al., 2014; Klein, Jansen, Kittler, & Reich, 2015). Other identified direct sources
103 include non-poultry meats, raw seafood, unpasteurized dairy products, and untreated surface-water
104 supplies, with an increasing recognition also of environmental sources and direct contact with animals,
105 especially in the developing world (FAO/WHO, 2009).

106
107 In a recent European Union (EU) baseline study, 71% of broiler batches were *Campylobacter*-positive
108 at slaughter, although the range by Member State was 2% to 100% (EFSA, 2010a). A summer peak in
109 incidence was evident, most markedly in more northern latitudes, and the UK data showed the summer
110 months to be associated with an elevated risk of heavily contaminated carcasses (Powell et al., 2012).

111 Season or average temperature have proven to be significant risk factors in several other studies (Allain
112 et al., 2014; Chowdhury, Sandberg, Themudo, & Ersbøll, 2012; Georgiev, Beauvais, & Guitian, 2017;
113 Sandberg et al., 2015; Smith et al., 2016; Sommer et al., 2016). *Campylobacter* bacteria colonize
114 broiler flocks asymptotically, with rapid spread within a flock evident from the time of first
115 detection. There is very little evidence for vertical transmission of *Campylobacter* from experimental
116 and epidemiological studies (Agunos, Waddell, Léger, & Taboada, 2014), and detectable colonization
117 of flocks commonly occurs around three to four weeks of age, and rarely before two weeks (Hansson,
118 Engvall, Vågsholm, & Nyman, 2010; Hermans et al., 2011; T. Humphrey, Paulsen, Pfeifer, &
119 Smulders, 2012).

120

121 The timing of flock exposure to *Campylobacter* is a matter of some uncertainty and there is subtyping
122 evidence of carryover from previous flocks in a minority of UK cases, and elsewhere (Damjanova et
123 al., 2011; Newell et al., 2011; Strachan et al., 2015; Zweifel, Scheu, Keel, Renggli, & Stephan, 2008).
124 In Finland, sequential positive flocks from the same farm tend to have closely related *Campylobacter*
125 strains (Llarena, Huneau, Hakkinen, & Hänninen, 2015), whereas more diverse strains are seen when
126 intervening flocks are un-colonized. Two Danish studies have identified the previous flock in a house
127 being *Campylobacter*-positive as a risk factor for flock colonization, suggesting carryover or a
128 persistent local source (Chowdhury et al., 2012; Sandberg et al., 2015). Viable *Campylobacter* were
129 recovered from internal access areas of Irish cleaned empty houses just before flock placement, and
130 from feeders and drinkers less than a week later (Battersby, Whyte, & Bolton, 2016b).

131

132 Interestingly, longer downtimes between flocks have been identified as a positive risk factor in recent
133 UK and international (EU) studies (Georgiev et al., 2017; Høg et al., 2016; Sommer et al., 2016). There
134 appears to be an inverse association between length of downtime and the quality of hygiene and/or
135 more general turn-around procedures. Furthermore, longer downtime provides increased opportunity

136 for environmental *Campylobacter* organisms to enter empty houses via farm pest vectors, and less
137 productive farms (with possibly poorer biosecurity) can more frequently have longer downtimes if
138 they are preferentially taken out of production at times of lower demand (Sommer et al., 2016).

139

140 Despite chicks being susceptible to experimental colonization from a very young age, it may be that
141 colonization under commercial field conditions occurs only when the amount of maternal antibody is
142 sufficiently low (Vandeplas, Dubois, Beckers, Thonart, & Thewis, 2009). Alternatively, birds might
143 become colonized in the field when very young (perhaps not in the parts of the intestinal tract that are
144 typically sampled), but not start shedding detectable numbers of the organism until around three weeks
145 of age (Ingesa-Capaccioni et al., 2016; Yano et al., 2014). By whichever route initial colonization of
146 one or more birds occurs, subsequent intestinal multiplication of the organism and shedding of large
147 numbers (up to 10^9 colony-forming units [cfu] per gram of feces) appears to ensure rapid horizontal
148 spread throughout the rest of the flock (Cawthraw, Wassenaar, Ayling, & Newell, 1996; Hermans et
149 al., 2011). The age of a flock at slaughter is significantly positively associated with the risk of it being
150 *Campylobacter*-positive (Chowdhury et al., 2012; EFSA, 2010b), lending weight to the view that the
151 eventual status of a flock is strongly related to the cumulative risk of exposure to a colonizing dose by
152 one or more individuals during the lifetime of the flock.

153

154 Peak shedding occurs between three and seven weeks of age, that is, throughout the latter part of the
155 broiler rearing cycle (Agunos et al., 2014). In the longer term, a pattern was observed in a free-range
156 breeder flock of individual strains (sequence types) of *C. jejuni* rapidly achieving high prevalence and
157 then tailing off over several weeks, whilst overall shedding remained fairly constant as other strains
158 exhibited similarly transient periods of dominance (Colles, McCarthy, Bliss, Layton, & Maiden, 2015).
159 By contrast, *C. coli* strains in the same study were less numerous and tended to be more persistent,
160 with a lower peak prevalence of shedding individuals. Another long-term study (Ingesa-Capaccioni

161 et al., 2016) also showed a sustained high individual-level prevalence of shedding over a breeding
162 flock cycle.

163

164 Observations and models of consumer risk, from producer through slaughter and processing stages of
165 the broiler meat chain, have suggested that reducing the flock-level prevalence of *Campylobacter*
166 colonization would have an approximately equivalent effect on consumer risk. That is, a 50% reduction
167 in flock prevalence would yield a 50% reduction in consumer risk (FAO/WHO, 2009). There may also
168 be a synergistic effect with reduced individual-level prevalence within affected flocks at slaughter.
169 The density of contamination on a carcass and in the cecum may be linked, with higher counts in the
170 cecum being associated with highly contaminated carcasses (Hue et al., 2011; Rodgers et al., 2017). If
171 the degree of carcass contamination can be decreased by two log₁₀ units, the risk of human infections
172 via chicken meat may decrease 30-fold (Rosenquist, Nielsen, Sommer, Nørrung, & Christensen, 2003).
173 These considerations, allied with the likelihood of indirect routes of consumer exposure from
174 *Campylobacter*-positive broiler flocks, places a strong emphasis on the potential public health benefits
175 of reducing the incidence of *Campylobacter*-positive birds entering slaughterhouses, ideally by
176 preventing or delaying flock colonization. Field evidence of a negative effect of flock colonization
177 upon economic performance (McKenna et al., 2017) reinforces the desirability of addressing the issue
178 at the producer stage.

179

180 Many risk factors found to be significant in investigations using multivariable models involve
181 biosecurity and hygiene. For example: other livestock (particularly other poultry, cattle, and sheep)
182 on-farm or nearby, larger numbers of broiler houses on-site (particularly if mixed flock ages), larger
183 numbers of staff, more than one person entering a house during rearing, hygiene procedures on entering
184 houses, use of dedicated equipment for houses, general untidiness, drinking water (sources, sanitation,
185 and presence/absence of reservoirs on drinkers), and thinning (partial depopulation) of flocks near final

slaughter age (Chowdhury et al., 2012; EFSA, 2010b, 2011; Hansson et al., 2010; Høg et al., 2016; Newell et al., 2011; Sommer et al., 2016; Torralbo et al., 2014). Russa et al. (2005) have questioned the significance of thinning once flock age and season have been taken into account, but other studies have shown clear evidence of *Campylobacter* contamination of staff and of mobile thinning crews (Morris & Allen, 2009; Newell et al., 2011), indicating that personnel and thinning equipment hold substantial potential for breaches of biosecurity and for local dissemination of *Campylobacter* organisms (Agunos et al., 2014). Furthermore, a three-year UK survey of broiler slaughter batches identified previous partial depopulation as a risk factor for *Campylobacter* colonization independent of the strong age and seasonal effects (Lawes et al., 2012).

Intensive sampling at the end of the rearing cycle has shown heavy contamination of drinkers and feeders (Schroeder, Eifert, Ponder, & Schmale, 2014). Older broiler houses (Chowdhury et al., 2012; Høg et al., 2016; Sommer et al., 2016) and the ventilation system employed (Sandberg et al., 2015) are also associated with increased risks, which may relate to some biosecurity and hygiene factors. Indeed, one six-country EU study indicated that certain biosecurity measures (presence of anteroom and hygiene barrier, non-shared tools) were protective only in the context of newer houses (Sommer et al., 2016). Features that might be expected to be protective, such as boot dips, prolonged downtime, and lower stocking density, can sometimes appear as positive risk factors (Høg et al., 2016; Sommer et al., 2016), probably owing to deficient implementation or associations with poorer hygiene or biosecurity. Feed and fresh litter, which are dry and thus not conducive to *Campylobacter* survival, have not commonly yielded the organism (Agunos et al., 2014), neither have they been shown to pose a significant risk (Adkin, Hartnett, Jordan, Newell, & Davison, 2006). A study of seven breeder flocks (kept under enhanced biosecurity) identified the onset of *Campylobacter* colonization much later than broilers, at between 12 and 16 weeks, and peaking only after transfer to laying houses at 20 weeks (Ingresa-Capaccioni et al., 2016).

211

212 *Campylobacter* organisms' lack of identified global stress response capacity and their apparent
213 susceptibility to environmental stresses such as heat, oxygen, dryness, and osmotically active solutes
214 (Bronowski, James, & Winstanley, 2014; Ganan, Silvan, Carrascosa, & Martinez-Rodriguez, 2012)
215 may be counteracted by their genetic diversity, facilitated by a high frequency of DNA rearrangement
216 and exchange (Bronowski et al., 2014; de Zoete, van Putten, & Wagenaar, 2007; Scott, Timms,
217 Connerton, El-Shibiny, & Connerton, 2007). Furthermore, there is some evidence that poultry-related
218 strains commonly are exceptionally tolerant of aerobic conditions (Oh, McMullen, & Jeon, 2015;
219 O'Kane & Connerton, 2017). They can be surprisingly persistent in certain environmental niches,
220 including in drinking water supplies, and when co-located with other micro-organisms such as in
221 biofilms or protozoal hosts (Agunos et al., 2014; Bronowski et al., 2014; Burbarelli et al., 2017; T.
222 Humphrey et al., 2012; Whiley, van den Akker, Giglio, & Bentham, 2013). This, together with a wide
223 range of host species that allow multiplication and shedding, presents a persistent environmental
224 reservoir to challenge biosecurity and hygiene defenses. Free-range and organic flocks, which are
225 reared outdoors and to a greater age than conventional broilers, have a higher risk of *Campylobacter*
226 colonization, with more limited options for enhancing biosecurity (EFSA, 2011).

227

228 Investigations into routes of contamination have thus far been hampered by the variation and instability
229 of the *Campylobacter* genome, plus the frequent existence of multiple *Campylobacter* genotypes
230 within the same flock, which together make relatively blunt instruments of the established genetic
231 subtyping techniques, for example *fla*-typing, pulsed-field gel electrophoresis, and multi-locus
232 sequence typing (Agunos et al., 2014; Messens, Herman, De Zutter, & Heyndrickx, 2009). The advent
233 of practical whole-genome sequencing techniques, enhanced multi-locus typing, and metagenomic
234 approaches will likely make an impact in this area (Cody, Bray, Jolley, McCarthy, & Maiden, 2017).

235

236 Much of the substantive work on anti-*Campylobacter* measures in poultry up to the start of the present
237 decade was summarized by Hermans et al. (2011) and in the European Food Standards Agency
238 Scientific Opinion (EFSA, 2011). Interventions to improve biosecurity and hygiene, both proposed
239 and practiced, aim to completely prevent flock colonization by *Campylobacter*, as current methods to
240 suppress shedding and colonization within a flock, once the organism has become established, appear
241 to be largely ineffective (EFSA, 2011). Complementary measures to increase flock resistance to
242 colonization have also been tested and include: antimicrobial substances administered in water or feed,
243 probiotics, vaccination, and breeding for decreased susceptibility. Some of these approaches, plus
244 bacteriocin or bacteriophage treatments and prebiotic preparations, have also been used in colonized
245 birds in attempts to reduce shedding or viability of *Campylobacter* by the time of slaughter.

246

247 ***Field investigations into biosecurity and hygiene***

248 Some reports include both field and small-scale trials and some interventions have only been evaluated
249 on a small scale, but some such trials illustrate features that are highly relevant to potential commercial-
250 scale applications. Where appropriate, these smaller trials are discussed. Reported large-scale
251 interventions may be categorized loosely as follows: biosecurity and hygiene during rear; biosecurity
252 and hygiene during catching/thinning, transport, and lairage; other measures around transport.

253

254 **The rearing phase**

255 An early investigation into the value of an enhanced hygiene barrier was reported by T. Humphrey et
256 al. (1993), who focused on boot-dipping stations on a three-house commercial unit. When phenolic
257 disinfectant concentration was increased from 1 to 3% and the usual internal door boot-dipping stations
258 were supplemented by external door stations, flock colonization by *Campylobacter* did not occur in

one instance and was delayed by two to three weeks (compared with contemporaneous control flocks) in the other three instances. All control flocks were colonized early, by 10 days of age.

Van de Giessen et al. (1992; 1998) reported biosecurity and hygiene interventions introduced at defined time points during longitudinal studies of sequential rearing cycles. One farm, with previously low standards of hygiene, introduced improved cleaning & disinfection (C&D), footbaths, dedicated clothing and boots, a hygiene barrier, hand washing, enhanced vermin exclusion and control, plus fencing and concreting of the farm yard. *Campylobacter* did not colonize the following three flocks in the study house at any stage to slaughter, despite the organism being isolated from the preceding seven (van de Giessen et al., 1992). On two other farms, with three and two study houses, respectively, similar measures to those above were introduced between rearing cycles. The proportion of flocks colonized by *Campylobacter* as assessed by feces sampling a few days before slaughter dropped from 67 to 22% (12/18 to 2/9) in one case, and from 100 to 42% (4/4 to 5/12) in the other (van de Giessen et al., 1998).

Another field study similarly introduced a number of hygiene and biosecurity measures between the first and second of three sequential monitored flocks in each of two houses on a North American unit (Dale, Nolan, Berghaus, & Hofacre, 2015). These included physical hygiene barriers, alcohol gel hand-rubs, strict personnel access restrictions, dedicated equipment for houses, enhanced procedures for each of C&D, insect plus rodent control, improved fencing, and litter disposal, plus an extended (three-week) downtime. However, no effect on the age of flock colonization by *Campylobacter* was seen subsequently. It was notable that *Salmonella* also was present, and in some flocks from placement, suggesting that there may have been problems with biosecurity and hygiene in the earliest stages of the flock life.

284 Biosecurity, and hygiene measures were examined on a wider scale by Gibbens et al. (2001), who
285 selected one intervention house on each of 13 UK multi-house commercial sites operating an all-in-
286 all-out policy, plus 25 associated control houses. A single flock in each house was monitored for flock
287 colonization by *Campylobacter*. Enhancements were instituted with respect to: C&D before flock
288 placement, boot dipping (changed to phenolic agent and altered locations), the use of dedicated boots
289 and overalls within the house, construction or delineation of a ‘hygiene barrier’ defining the ‘clean
290 area’ of the anteroom, and use of hand sanitizer. In addition, regular compliance reminders were issued
291 and assessments of the same were made. There was strong evidence of benefits, in terms of delayed
292 colonization and reduced prevalence of *Campylobacter*-positive flocks at slaughter age, although
293 conventional 95% statistical significance was not demonstrated. Nonetheless, control flocks were nine
294 times more likely than intervention flocks to be colonized by slaughter age.

295

296 Factors potentially limiting the statistical power of the above study included: the modest number of
297 test flocks, the observation that interventions were not wholly implemented for all test flocks and were
298 applied, to some extent, in many control flocks, and an unexplained ‘company effect’, wherein all
299 flocks operated by one of the three companies involved proved *Campylobacter*-positive, regardless of
300 intervention. Tentatively, the findings were interpreted as pointing towards a potential biosecurity- and
301 hygiene-driven reduction from the then UK flock *Campylobacter* prevalence at slaughter of around
302 80%, to around 40%.

303

304 Another UK study (Georgiev et al., 2017) investigated enhanced biosecurity on sixteen farms with
305 respect to equipment, clothing, and entry/exit procedures, but measured outcomes by levels of cecal
306 *Campylobacter* at slaughter rather than by presence/absence in the flock. This showed a highly
307 significant association between biosecurity interventions and a lower *Campylobacter* count
308 ($<10^{5.09}$ cfu/g), compared with control premises. An observational study in Ireland (Smith et al., 2016)

309 demonstrated significant positive correlations between a high farm biosecurity audit score and both of:
310 a lower prevalence of *Campylobacter*-positive birds at slaughter, and lower numbers of *Campylobacter*
311 in the cecum among positive birds. This correlation was only observed at first thinning, suggesting
312 that the catching and partial depopulation process may have deleteriously affected the on-farm
313 biosecurity. Among units with poorer biosecurity, a physical access barrier and dedicated footwear
314 were protective risk factors. In both the foregoing studies, the association with superior biosecurity
315 was lower, or absent, following thinning (Georgiev et al., 2017; Smith et al., 2016).

316

317 Studies on biosecurity, such as the one by Gibbens et al. (2001), often encounter difficulties in
318 recruiting and randomizing broiler houses, and in enforcing a range of sometimes disruptive trial
319 measures in a commercial setting. A descriptive paper (Pattison, 2001), written from the standpoint of
320 a commercial operator and linked to the study by Gibbens et al. (2001), offered the opinion that
321 effective hygiene barriers, especially those that offered physical obstruction to the passage of
322 equipment, were the most important anti-*Campylobacter* measures. However, hygiene procedures
323 needed to avoid being too onerous if they were to be consistently applied. A risk factor study in Sweden
324 emphasized the importance, and modest cost compared to structural alterations, of rigorous hygiene
325 procedures on entering and leaving houses (Hansson et al., 2010). The use of two changes of footwear
326 at suitable hygiene barriers either side of the anteroom, as commonly practiced in Sweden, was
327 suggested as being less demanding of time and effort than thorough and prolonged disinfection of
328 boots, and appeared to be a protective factor.

329

330 Another description of the possible effects of enhanced biosecurity and hygiene during rearing arose
331 out of a two-year study on the practice of thinning (Allen, Weaver, et al., 2008; Morris & Allen, 2009).
332 In the first year (June to November) 50% of flocks (12/24) were *Campylobacter*-positive. In the second
333 year (February to September) the equivalent proportion was 33% (9/27), albeit among different flocks.

334 This followed tightening of biosecurity and hygiene (increased physical hygiene barriers and
335 disinfectant footbaths) in response to the threat of avian influenza and a *Campylobacter* information
336 campaign. However, it is unclear from the two reports whether these differing proportions of
337 *Campylobacter*-positive flocks were determined at the time of thinning or in the period after thinning.

338

339 A novel approach has been described recently by Battersby et al. (2016a), wherein small groups of
340 chicks were reared in plastic-walled pens within commercial broiler houses, sharing airspace, feed,
341 and water lines with the surrounding flock but having no direct contact with farm personnel or other
342 birds. All flocks were eventually *Campylobacter*-positive, but colonization of the penned birds was
343 prevented, in four of five cases, and delayed by two weeks in the remaining case. Several factors may
344 have contributed to these effects, including the lack of contact with personnel.

345

346 Recent brief reports of biosecurity field intervention studies in Spain (Cerdeira-Cuellar et al., 2015) and
347 the UK (Strachan et al., 2015) have indicated apparent benefits in terms of *Campylobacter* isolations
348 from test versus control premises. However, thinning appeared to counteract gains in the Spanish
349 study, whilst general improvements in management on control farms in the UK may have reduced the
350 observed difference between intervention and control premises.

351

352 In response to correlation between housefly numbers and the seasonal peak in prevalence of
353 *Campylobacter*-colonized flocks in Denmark, fitting of fly screens to all potential entry points has
354 been subjected to trials, in a targeted biosecurity intervention. Initial trials, conducted during summer
355 months, monitored 52 test flocks on 11 farms, with 70 control flocks on 13 separate farms (Hald,
356 Sommer, & Skovgard, 2007). Strikingly, only 15.4% of test flocks were colonized by the end of the
357 rearing phase, compared with 51.4% of control flocks. A four-year trial followed, using paired
358 intervention and control houses on the same farms (Bahrndorff, Rangstrup-Christensen, Nordentoft,

359 & Hald, 2013). This confirmed that fly screens were associated with the disappearance of the summer
360 rise in incidence of *Campylobacter*-colonized flocks, and that the overall proportion of test flocks
361 colonized by the time of slaughter (10.3%) was significantly lower than the control flocks (41.4%). It
362 was estimated that 72% of Danish flock breakdowns could be prevented by this measure, provided that
363 the high hygiene and biosecurity measures already in place in the test houses were maintained, and
364 that ventilation systems could be altered to compensate for airflow restrictions imposed by the fly
365 screens.

366

367 A similar approach has been tried with 35 commercial houses in Iceland. In 2008 all houses on four
368 ‘problem’ sites were fly-screened, and over the course of the summer, the incidence of *Campylobacter*-
369 positive flocks dropped by 62% over baseline data. For one company, colonized flocks fell from 48.3%
370 to 25.6%, whilst in the other company the proportions fell from 31.3% to 17.2% (EFSA, 2011;
371 Lowman et al., 2009; Moore & Matsuda, 2010). Fly screens also appeared to have made a distinct
372 contribution to improved *Campylobacter* status on five Spanish farms in an intervention study, but
373 only once general biosecurity had been improved (Cerdeira-Cuellar et al., 2015). Evidence has been
374 presented of a risk posed by flies in the UK, with respect to both broiler house ingress and carriage of
375 viable *Campylobacter* organisms (Royden et al., 2016). Whilst protection of birds from exposure to
376 *Campylobacter* via insects is likely to be realized only in the context of other stringent biosecurity
377 measures, these findings are powerful evidence of the likely significance of this route of flock exposure
378 in certain circumstances.

379

380

381 Reports of *Campylobacter*-focused assessments of terminal hygiene are sparse, but Battersby et al.
382 (2017) commonly found viable organisms in access areas and on feeders and drinkers shortly after
383 disinfection in one field study. ‘Dry’ application of agents by fogging was far more effective than

384 spraying disinfectant solutions. A related study (Battersby et al., 2016b) found viable *Campylobacter*
385 organisms in staff access areas of houses just before flock placement, but not from bird
386 accommodation. Burbarelli et al. (2017) examined environmental contamination following an
387 enhanced C&D regime in an experimental facility; they reported that *Campylobacter* was still
388 recovered from water in the drinker supply despite flushing the system with disinfectant. Follow-on
389 flocks were similarly colonized by *Campylobacter* regardless of whether enhanced or control C&D
390 techniques were used.

391

392 **Catching and transport**

393 Racicot et al. (2013) examined hand-sanitizing protocols for a thinning crew in the field, and they
394 concluded that those with a degreasing element (soap or cream) were most effective with anything
395 other than light soiling, although *Campylobacter* contamination was not specifically examined.
396 Protocols with warm water and soap were preferred by operators, which may be significant for
397 compliance. An observational study of thinning crews on 51 UK farms (Allen, Weaver, et al., 2008;
398 Morris & Allen, 2009) found evidence, via bacteriological sampling, of frequent *Campylobacter*
399 contamination of crews' vehicles, hands, and footwear before thinning commenced. Furthermore,
400 crews' footwear was commonly not of a type suitable for immersion in disinfectant. Pulsed-field gel
401 electrophoresis subtyping studies of strains on seven of the farms that became *Campylobacter*-positive
402 after thinning indicated that particular strains had spread from one farm to another when the farms
403 were jointly owned by the same company and employed the same bird-catching teams and/or vehicles
404 (Allen, Weaver, et al., 2008). In response to the threat of avian influenza and a UK biosecurity
405 information campaign, there was a tightening of catchers' hygiene and biosecurity (increased changing
406 of protective clothing, increased disinfection of vehicles) in the second year of this two-year study.
407 This was associated with a reduction in the proportion of *Campylobacter*-positive samples for all of

408 the fourteen environment and operator sample types, although in no cases did the proportion reduce to
409 zero (Allen, Weaver, et al., 2008).

410

411 Multivariable regression analysis conducted on the large EU baseline study dataset indicated a
412 significant effect of thinning, in addition to effects of flock age and season. An independent
413 multivariable analysis on UK data collected at the same time also concluded that thinning was a risk
414 factor separate from flock age (Lawes et al., 2012). Other quantitative analytical studies have
415 implicated thinning in counteracting the reduced colonization associated with enhanced biosecurity,
416 among the birds remaining at final depopulation (Georgiev et al., 2017; Smith et al., 2016). By contrast,
417 a retrospective multivariable modelling analysis of data from The Netherlands concluded that thinning
418 was not significantly associated with flock colonization by *Campylobacter* once flock age and season
419 had been accounted for (Russa et al., 2005). However, there may be differences between countries in
420 the hygiene and biosecurity practices around thinning. Moreover the retrospective nature of the
421 analysis means that, as the authors themselves note, their findings require validation by prospective
422 studies. Barrier methods to separate thinned sections of the house from remaining birds for a period
423 after entry of catching teams have been suggested but not evaluated in practice (Davies, 2005).

424

425 The effect of pre-existing contamination on surfaces of transport crates was examined in a commercial
426 setting by Rasschaert et al. (2007), who reported that around 70% of the crates examined carried
427 multiple strains of *Campylobacter* 12 hours or more after C&D. Furthermore, three of four flocks
428 transported in these crates acquired *Campylobacter* contamination on external body surfaces between
429 final sampling on-farm (breast feathers and skin swabbed one hour before depopulation) and sampling
430 an hour before slaughter. Intestinal tract samples from these flocks were *Campylobacter*-negative at
431 slaughter. Other studies, where transport crates and transporters have been sampled in the field before
432 use, concur that residual contamination of transport equipment is a common problem.

433

434 Other investigations, by Allen et al. (2008), used an experimental crate-cleaning rig in field
435 (slaughterhouse) environments and concluded that visual cleanliness did not correlate well with
436 measured reductions in aerobes or Enterobacteriaceae. Cleaning regimens that used brushing or
437 ultrasonic agitation and higher wash-water temperatures appeared most effective, but practical
438 elimination of bacterial contamination by current methods appeared to be an unlikely prospect under
439 commercial conditions, with features such as surface damage and biofilms presenting additional
440 challenges to sanitization. Furthermore, the modules used to hold crates in the field are even more
441 difficult to clean effectively than the crates themselves.

442

443 A laboratory-scale attempt to hasten decontamination of crate surfaces by application of a desiccant
444 (corn starch powder) suggested that application of the agent enhanced the reduction of *Campylobacter*
445 numbers for up to two or four hours after application, on washed and unwashed surfaces, respectively
446 (Berrang, Meinersmann, & Hofacre, 2011). However, efficacy remains unexplored in field situations
447 in the presence of natural contamination.

448

449 Commercially-sourced *Campylobacter*-positive broilers were used in a small-scale trial examining the
450 effect of raised mesh flooring in transport crates as an attempt to limit fecal soiling and horizontal
451 transmission of enteric organisms during transport (Buhr, Cason, Dickens, Hinton, & Ingram, 2000).
452 Although visible soiling of breast feathers was noticeably reduced by the intervention, neither the
453 frequency of *Campylobacter*-positive carcasses (before and after de-feathering), nor the number of
454 such organisms per carcass, was significantly reduced in association with the altered flooring.
455 Interestingly, carcass counts of other microbes (coliforms, *E. coli*, and total aerobes) correlated poorly
456 with *Campylobacter* counts. Other work similarly has found no correlation between bird fecal soiling

457 on arrival at the slaughterhouse and carcass *Campylobacter* counts (Koene, de Jong, van der Goot,
458 Wagenaar, & den Hartog, 2017).

459

460 **Psychological and training considerations**

461 Recent assessments of biosecurity and hygiene understanding and practice by producers have
462 identified substantial room for improvements. A Canadian survey of producers identified issues of
463 poor biosecurity around placing and thinning crews and visitors, plus a poor understanding of the
464 significance of *Campylobacter* colonization in flocks (Young et al., 2010). Field assessments by a
465 Belgian group similarly identified much variation in practice and scope for improvements (Gelaude,
466 Schlepers, Verlinden, Laanen, & Dewulf, 2014), whilst a recent large-scale investigation among
467 European broiler units identified measures relating to visitors and staff to be the least well-
468 implemented aspect of ‘external’ biosecurity (Van Limbergen et al., 2018).

469

470 Racicot et al. (2011, 2012a, 2012b) have performed structured investigations into operator behavior
471 focused upon entry into Canadian poultry houses, providing an unusually detailed and objective insight
472 into this combination of human behavior and hygiene under field conditions . In one study, operators
473 on eight broiler farms were aware that a study into human traffic was being performed, and visible
474 cameras were installed in houses, but they were not aware either of hidden cameras in ante rooms, or
475 that the focus of the study was on biosecurity practices (Racicot et al., 2011). Posters detailing the
476 existing biosecurity rules specific to that farm were displayed in ante rooms, and cameras were then
477 monitored continually for two two-week periods, with an intervening six-month gap. The principal
478 measures to be followed were the changing of footwear (or donning of overshoes) without cross-
479 contamination of demarcated zones, and the changing of outer clothing. The investigators reported
480 (amongst other things) that fewer than 3% of house visits were free of procedural errors, that violations
481 of the hygiene barrier were common, that short visits were associated with poorer compliance, that

482 compliance deteriorated over time, and that there were a variety of visitors entering houses including
483 family members of staff and people who could not be identified. Of the five most common breaches
484 of biosecurity, four were major violations of hygiene barriers (that is, ignoring barriers between clean
485 and contaminated areas, completely failing to change footwear, to don overalls or to wash hands) and
486 the other was a failure to log visits, this last error occurring on 70% of occasions.

487

488 A second study, using a similar approach but comparing test with control farms, examined the effects
489 of a visible camera in entrance areas versus an audit process (involving written notifications, self-
490 assessments, and investigator visits) upon compliance with pre-existing biosecurity practices on 24
491 poultry units (Racicot et al., 2012a). Whilst the presence of a camera had a strong immediate effect
492 upon compliance with changing footwear and respecting demarcated hygiene boundaries, after six
493 months the overall effect was not significant. The audit process had no overall significant effect and
494 revealed employee self-assessments to be commonly unrealistic with respect to their observed
495 biosecurity practices. By contrast, an ‘audit effect’ was postulated by Sandberg et al. (2017) following
496 observation of a correlation between proximity (+/- 60 days) to a biosecurity audit visit under the
497 Danish quality assurance scheme and negative flock *Campylobacter* status at slaughter.

498

499 Multivariable analyses by Racicot et al. (2012a) examined various factors, both in relation to the
500 number of required biosecurity measures truly respected on a specific visit and in relation to specific
501 biosecurity procedures. At the start of the study, factors associated with compliance overall were:
502 longer visits (positive) and being a farmer’s family member or having an observer present (negative).
503 After six months, longer visits, the presence of more houses on the farm, and the requirement for more
504 than five procedures were positively associated with compliance. Factors associated with increased
505 compliance with specific procedures included: longer visits, morning visits, a physical hygiene barrier,
506 ‘easy’ hygiene facilities, using over-boots versus changing boots, and more houses present per farm.

507 Negative associations were seen with: farmer's family members and (interestingly) the presence of the
508 farmer or another observer.

509

510 The personality traits, experience, training, and educational history of workers were also examined by
511 Racicot et al. (2012b) in relation to biosecurity compliance during entrance and exit from houses in
512 the same 24-farm study described above. Interestingly, in this local sample of Canadian producers,
513 51% of non-managerial employees and 42% of farm managers had not completed a high school
514 education, and corresponding values for a formal education in animal production were only 6.4 and
515 14%, respectively. Poultry educational meetings were attended by just 17% of employees, compared
516 with 65% of managers. Boot biosecurity compliance was associated with educational level among
517 farm employees and visitors. However, when everyone, including farmers and supervisors, was
518 considered, general education was no longer significant, whereas a formal industry education was.
519 Experience in the poultry industry for five to 11 years had the strongest positive association with boot
520 compliance, suggesting that initial training (less than five years' experience) was poorly effective and
521 that the attitudes of longer-standing employees (more than 11 years' experience) may have reflected
522 previously more lax industry standards of biosecurity. In the same study, two personality traits relating
523 to conscientiousness ('responsibility' and 'complexity') were positively associated with boot and
524 general compliance, respectively. An 'action-orientated' personality trait (indicating an energetic,
525 problem-solving approach to physical challenges and constraints) was also positively associated with
526 boot and general compliance.

527

528 A UK study of the practicalities and attitudes around thinning crews (Millman et al., 2017) suggested
529 that training is effective in imparting awareness and understanding of biosecurity hazards and
530 practices, but that there are many barriers to good implementation. These include: inconsistency in the
531 amount and quality of training offered, a tendency to 'learn on the job' and devise individual practices,

532 the substantial physical challenges of the task (teams of four to six catching and loading 5,000 to 6,000
533 grown birds per hour, in warm conditions) leading to cumbersome or hot protective clothing being
534 omitted, work schedules that are unrealistic with respect to decontamination procedures, and
535 skepticism among farm managers about the benefit of painstaking biosecurity measures.

536

537 ***Interventions complementary to biosecurity and hygiene***

538 Some reports include both field and small-scale trials, some interventions have only been evaluated on
539 a small scale, and some small-scale trials illustrate features that are highly relevant to potential
540 commercial-scale application. Where appropriate, these smaller trials are discussed. Reported large-
541 scale interventions fall roughly into the following categories: measures relating to transport, drinking
542 water sanitation, antibacterial treatments delivered via drinking water and/or via feed, bacteriocins or
543 bacteriophage administration, pre- and pro-biotics, and litter acidification. Interventions and trial
544 outcomes are summarized in Table 1.

545

546 **Procedures around transport**

547 The effect of feed withdrawal (12 hr) and simulated transport (1 hr, plus 8 hr lairage) was investigated
548 on a small scale using naturally-colonized commercial birds (Northcutt, Berrang, Dickens, Fletcher,
549 & Cox, 2003). This study reported a significant, but small (around 0.4 log₁₀ units), elevation in
550 *Campylobacter* counts in pre-chill carcass rinsate among birds that were subjected to the procedures,
551 compared with those that were not starved and which were transported a short distance before being
552 slaughtered immediately. An apparently protective effect of longer ('more than 2.5 hr') transport upon
553 cecal *Campylobacter* status (Lawes et al., 2012) may owe more to an association between transport
554 distance and company size than to a causal relationship, as discussed by the authors. Lairage time in

555 excess of 1 hr was a risk for positive cecal *Campylobacter* status in Costa Rica (Zumbado Gutiérrez &
556 Romero Zúñiga, 2017).

557

558 **Acidic water treatments**

559 The acidification of drinking water may be used throughout rearing or targeted around the time of
560 catching and transport. In the latter mode, the aim is to reduce the spread and multiplication of
561 *Campylobacter* by decreasing survival of the organism in the upper alimentary tract, particularly the
562 crop. Pre-slaughter feed withdrawal has been associated with increased colonization in the crop by
563 *Campylobacter* (Byrd et al., 1998). Lactic acid was introduced into the drinking water (final pH around
564 3) of seven commercial flocks, starting one hour before the beginning of a 10- to 14-hr pre-slaughter
565 feed withdrawal (Byrd et al., 2001). Compared with paired control flocks from the same farms, there
566 were overall significantly fewer *Campylobacter*-positive crop contents at slaughter and fewer
567 *Campylobacter*-positive pre-chill carcasses among treated birds. However, differences were modest,
568 and when analyzed farm by farm, differences were found not to be significant on four of the seven
569 farms.

570

571 Commercial acidifier preparations have also been examined. Haughton *et al.* (2013) used a product
572 (‘PWT’) that has a claim of high potency with minimal palatability issues in a four-farm field trial,
573 with a small subset of 20 birds per flock assigned to each of two interventions. *Campylobacter* cells
574 were enumerated in cecal contents at slaughter. In general, no significant differences were seen
575 between untreated birds and birds that had received acidified water (pH 3.5), either just for the 24 hr
576 before slaughter or for the first week of life plus two days either side of feed changes and 24 hr before
577 slaughter. An effect of the product upon cecal pH was not observed in the field trial, nor was it seen
578 with *in vitro* tests where up to twice the recommended drinking water concentration was added directly

579 to cecal content. Field isolates of *Campylobacter* showed widely varying sensitivity *in vitro* to water
580 acidified with the product.

581

582 Another field trial was reported by Jansen *et al.* (2014), using a commercial mix of short- and medium-
583 chain fatty acids (SCFA, MCFA) giving a drinking water pH of 4.0 to 4.5. This treatment was used
584 throughout rearing, from placement to slaughter, using three consecutive co-housed test and control
585 flocks. There was no evidence that flock colonization by *Campylobacter* was delayed by the treatment.
586 Cecal counts at slaughter (five birds per flock on each of six thinning or final depopulation occasions)
587 were highly variable. However, on three of the six occasions the mean values were significantly lower
588 (by around 4 to 6 log₁₀ units) among test animals. No significant effect on *Campylobacter* counts on
589 the corresponding carcasses was seen, although the percentage of *Campylobacter*-positive carcasses
590 was high compared with that of positive ceca, suggesting there may have been substantial cross-
591 contamination at the slaughter plant.

592

593 Using two groups of around 40 broilers kept in three-bird cages, Gracia *et al.* (2016) examined the
594 inclusion in drinking water of blends of monoglycerides of three- to 12-carbon acids, with or without
595 additional free organic acid mixes. Water was treated throughout a 6-week rearing period, with oral
596 *C. jejuni* inoculation (10⁴ cfu) at 14 days of age and periodic *post mortem* sampling of 10-12 birds. No
597 suppressive effect of water treatment on cecal *Campylobacter* counts was found. Van Bunnik *et al.*
598 (2012) reported small-scale experimental trials using drinking water acidified to pH 4.0 with a blended
599 product, examining the possibility of prevention of infection earlier in the rearing phase. In an indirect
600 transmission model one of eight test birds individually-penned adjacent to birds orally inoculated with
601 *C. jejuni* was colonized two weeks later, compared with five of seven control birds, which represented
602 a significant reduction in transmission associated with use of the acid. However, there was no evidence

603 of protection afforded by the water treatment for birds in direct contact with seeder birds, suggesting
604 that any protection is limited to low-level challenge.

605

606 Capric and caprylic acids have been shown *in vitro* to be particularly potent inhibitors of *C. jejuni*
607 (Molatová et al., 2010). A small-scale trial, using groups of 10 birds, specifically examined a mixed
608 MCFA product (caproic, caprylic, capric and lauric acids), introduced as an emulsion into drinking
609 water (final pH 5.4) from one-day-old in an attempt to augment the upper alimentary tract barrier to
610 *Campylobacter* colonization (Hermans et al., 2012). The MCFA effectively killed *Campylobacter* in
611 the drinking water, and oral inoculation studies at two weeks of age suggested the threshold for
612 colonization after a single inoculum was increased in MCFA-exposed birds. However, cecal
613 colonization of initially *Campylobacter*-negative birds in groups exposed to inoculated seeder birds
614 five days before *post mortem* examination was not significantly different between test and control
615 groups. A further small-scale study of MCFA (Metcalf et al., 2011) examined birds inoculated with
616 *C. jejuni* at three days old then given the sodium salt of caprylic acid in drinking water for three days
617 before slaughter at two weeks of age. Suppressive effects on cecal *C. jejuni* counts were not identified
618 consistently, across a wide range of administered concentrations.

619

620 Hilmarsson *et al.* (2006) tested glycerol monocaprinate (the 1-monoglyceride of capric acid;
621 ‘monocaprin’), added as an emulsion to drinking water. Within 10 minutes of adding monocaprin
622 (2.5 mmol/L) to water inoculated with 10^6 to 10^7 cfu/mL *C. jejuni*, *Campylobacter* organisms were
623 not detectable by culture and the treated water did not transmit *Campylobacter* to birds. However,
624 5 mmol/L monocaprin in drinking water, and also sprayed on feed, did not prevent colonization of 24-
625 day-old broilers via seeder birds. A further trial, using naturally infected 36-day-old birds sourced from
626 a commercial flock and using a still higher monocaprin concentration (10 mmol/L) in drinking water
627 and sprayed on feed, showed a significant (1.5 to 2.2 log₁₀ units) reduction in cloacal swab

628 *Campylobacter* counts after three days, compared with initial counts and with control birds. However,
629 a consistent reduction in counts was not seen after a longer time, either using cloacal swabs (10 days)
630 or the potentially more-reliable cecal culture (13 days), and weight gain was depressed in test birds.

631

632 **Non-acid water treatments**

633 Chlorination has been studied in commercial-scale field situations. A revealing observational study in
634 New Zealand sampled drinking water extensively, from tanks, taps, lines, and drinkers, in 11 houses
635 run by two companies (Boxall et al., 2003). Despite an official target for free available chlorine of two
636 parts per million (ppm) in one company, the mean values obtained exceeded one-tenth of this (0.2 ppm)
637 in only three houses, and no mean values at drinkers exceeded 1 ppm. Thus, it was suggested, a
638 protective effect of water chlorination upon *Campylobacter* colonization may in many cases not be
639 observed simply because an adequate level of chlorination is not being achieved. Suspended solids,
640 biofilms, incorrect metering of additives, and habitual sampling of water only close to the water tank
641 may all contribute to limited freely available chlorine at drinkers. A laboratory study (Trachoo &
642 Frank, 2002) also demonstrated increased *C. jejuni* adherence to PVC surfaces and resistance to water
643 sanitizers when the organisms were grown with pre-existing biofilms formed by environmental
644 bacteria isolated from nipple drinkers (*Curtobacterium* spp.) and a meat processing plant
645 (*Pseudomonas* spp.). Thus, persistence of water system contamination between flocks may be an
646 under-estimated hazard.

647

648 Stern *et al.* (2002) examined the effect of chlorinating drinking water supplies (2 to 5 ppm chlorine,
649 monitored fortnightly) in two flocks in borehole water-fed houses on two farms, with paired control
650 houses. The farms had only modest hygiene arrangements (lacking protective footwear, disinfectant
651 boot dips, or hand-wash facilities for staff), and water chlorination had no discernible effect on the
652 onset (at three weeks of age) or intensity of *Campylobacter* shedding by the flocks. It seems likely, in

653 this case, that the limited hygiene and biosecurity measures resulted in introduction of *Campylobacter*
654 via routes unrelated to drinking water and drinkers, or a high challenge dose. Evidence that drinking
655 water sanitation is a significant protective factor for flock *Campylobacter* status has been provided by
656 risk factor analyses elsewhere (Torralbo et al., 2014).

657

658 Neutral electrolyzed oxidizing water (pH 6.2 to 7.5, containing reactive chlorine and oxygen species)
659 was tested as a drinking water additive on two farms for three rearing cycles, from flock placement to
660 final depopulation (Bügener, Casteel, Kump, & Klein, 2014). Treated water was free of detectable
661 *Campylobacter* throughout rear, whereas control water samples were uniformly contaminated by 35
662 days. Water treatment did not prevent flock colonization, but there were significantly fewer positive
663 cloacal swabs at 35 days of age, and significantly lower (around one to four log₁₀ units) counts of
664 *Campylobacter* were obtained from post-chill carcasses of test birds (five per flock), suggesting that
665 some inhibition of transmission within the flock, or delay of establishment of colonization, may have
666 lowered the *Campylobacter* load entering the abattoir. A small-scale trial with an antimicrobial
667 compound derived from garlic ('allicin') showed potentially useful anti-*Campylobacter* activity in
668 water *in vitro*. However, administration of allicin in the drinking water of chicks from shortly after
669 hatch failed to reduce their colonization by *C. jejuni* following oral inoculation at 14 days of age with
670 a dose of around 10³ cfu (Robyn, Rasschaert, Hermans, Pasmans, & Heyndrickx, 2013b).

671

672 **Acidic feed additives**

673 Acid treatment of feed has been reported in small-scale *Campylobacter* trials but not in commercial
674 settings. It may be perceived as desirable to prefer testing of water treatments, given that feed is not
675 an established medium for ingestion and spread of *Campylobacter*, and that feed is typically withheld
676 just before slaughter. In one feed study, an MCFA-rich distillate of palm oil ('Lodestar C8-C10') was
677 substituted for part of the oil component in feed and fed to hatchling broilers that were then challenged

678 orally with *C. jejuni* at two weeks of age (van Gerwe et al., 2010). Colonization of the birds was
679 monitored by sequential feces sampling, with *post mortem* examination two weeks later. Using a range
680 of inoculation doses, a 50% colonizing dose for birds on the acid-amended diet was calculated to be
681 $10^{4.8}$ cfu, around 2.3 log₁₀ units higher than for birds on a control diet.

682

683 Caprylic acid added to feed from one day of age was associated with transient suppression of the
684 numbers of *C. jejuni* organisms shed following oral challenge at 12 and 35 days old (Hovorková &
685 Skřivanová, 2015). However, feed intake was suppressed and cecal counts of *Campylobacter* at 42
686 days were not reduced. A similar, earlier, study (Molatová et al., 2011) used a capric/caprylic acid mix
687 in feed from one-day-old and oral challenge (with the same dose and strain as the previous study) at
688 two and four weeks. This study reported a reduction in cecal *Campylobacter* counts of around two
689 log₁₀ units at six weeks of age, irrespective of whether the acids were coated with a vegetable oil
690 preparation or not.

691

692 Five SCFA-based commercial products were included in a comparative trial with other feed additives,
693 using groups of around 45 broilers given feed treated according to manufacturers' recommendations
694 throughout rear, challenged with *Campylobacter jejuni* (10^4 cfu) at 14 days of age and subjected to
695 serial *post mortem* examinations (Guyard-Nicodème et al., 2016). One of these acid products, a
696 preparation of butyrate-coated microbeads, was associated with reduced cecal *Campylobacter*
697 concentration (1 to 2 log₁₀ units) on all three sampling occasions to four weeks post-challenge. Two
698 others were associated with significant but lesser reductions up to three weeks post-challenge.
699 Individual variation in cecal counts was wide, among both test and positive control birds. Using a
700 similar experimental protocol in a linked study (Gracia et al., 2016), a monoglyceride of MCFA
701 preparation added to feed from three to six weeks of age was associated with a reduced cecal

702 *Campylobacter* concentration (around one log₁₀ unit) up to the final six-week-old (four-week post-
703 challenge) sampling.

704

705 Using already-colonized birds, another study began feeding MCFA (capric, caprylic, caproic acid mix)
706 at 25 days of age, and it found no evidence of an effect on cecal *Campylobacter* counts three days
707 later, either using free acids or a preparation coated to enhance delivery to the large intestine (Hermans
708 et al., 2010). This study conflicts with earlier work reporting efficacious use of in-feed caprylic acid
709 in *Campylobacter*-positive market-age broilers (Solis de los Santos et al., 2009), for reasons which are
710 uncertain, but which may include differences in *Campylobacter* strain susceptibilities. Hermans *et al.*
711 (2010) also reported that intestinal mucus protected *C. jejuni* from inactivation by capric acid.

712

713 Thibodeau *et al.* (2014) reported a medium-scale trial (four 50-bird groups with commercial slaughter
714 conditions) using an encapsulated organic acid plus essential oil blend (principally formic and sorbic
715 acids plus thymol) added to feed from one day of age. Oral challenge with one of two two-strain mixes
716 of *C. jejuni* at two weeks was followed by slaughter one, two, and three weeks later. Cecal
717 *Campylobacter* counts were modestly reduced and increased at one and three weeks post-challenge,
718 respectively. Carcass contamination was significantly reduced only at three weeks post-challenge, by
719 0.9 log₁₀ units on average for both groups. The reduction was significant in only one of the two test
720 groups, where the mean difference was 1.4 log₁₀ units. It was postulated that strain differences may
721 have contributed to variation between the two test groups, also that the acids' effects on environmental
722 fitness of *Campylobacter* strains within slaughtered flocks may have resulted in reduced carcass
723 contamination even though cecal counts were increased.

724

Non-acid antimicrobials

A small trial using the ionophore coccidiostat salinomycin in feed found that it offered no protection to persistent colonization of 14-day-old birds by *C. jejuni* following a high dose (10^9 cfu) oral inoculum (Johansen, Bjerrum, Lund, & Pedersen, 2006). By contrast, a small-scale trial incorporating yolk (5% w/w) from eggs of hens immunized with adjuvanted *C. jejuni* lysate into chick feed (Hermans et al., 2014) demonstrated substantial protection against colonization following oral challenge with 10^4 cfu of the same strain of *C. jejuni* at 10 days of age. A reduction in cecal counts of more than five $\log_{10}$ units was observed in test animals at 13 days of age, and transmission to in-contact birds was prevented. However, *in vitro* tests of bacterial cell-binding by IgY-treated intestinal mucus suggested that colonization by heterologous *Campylobacter* strains may be less affected by the yolk antibodies.

Trials with the antimicrobial phytochemical thymol in small groups of naturally colonized slaughter-age birds showed a reduction of up to 1.5 $\log_{10}$ units in *Campylobacter* counts in the crop, but not ceca, of birds dosed 9 hr previously (Epps et al., 2015). Similar results were obtained when the conjugate thymol- β -D-glucopyranoside, which is more stable to foregut digestive processes, was used. It was hypothesized that thymol's anti-fermentive properties might be counterproductive with respect to *Campylobacter* inhibition in the large intestine and cecum. Two related studies (Gracia et al., 2016; Guyard-Nicodème et al., 2016) included essential oil, garlic, and herbal preparations in their comparative studies described above (under acid preparations in water and feed sections). None of the six products containing such components was associated with anything more than a transient reduction in cecal *Campylobacter* counts.

A plant-derived antimicrobial (carvacrol), which can be extracted from oregano oil, was shown to have inhibitory effects for adhesion and invasion of *Campylobacter* to chicken epithelial cells (Kelly et al.,

2017). When fed (120 to 300 mg/kg feed), it delayed natural colonization by *Campylobacter* in a 600-bird study, although cecal counts were similar to control birds by 35 days of age.

Diet structure

The addition of fibrous poorly digestible ‘structural’ material to the chicken diet has been tried in an attempt to slow passage of material through the acidic parts of the foregut (crop and gizzard) and to reduce ingestion of litter, thereby possibly elevating the gut barrier to *Campylobacter* and effectively reducing the challenge dose. A small-scale trial used test rearing diets with whole wheat or oat hulls as structural components, and inoculation with *C. jejuni* of one individual per eight-bird group at 32 days of age (Skånseng, Svihus, Rudi, Trosvik, & Moen, 2013). Monitoring of in-contact birds for 1 week after was performed by daily cloacal swabbing to day five, and *post mortem* examination. The test diets were associated with a significantly delayed spread of *Campylobacter* on days three to five post-exposure, and were enhanced in no-litter (rubber mat) flooring groups. The gizzard pH was also significantly lower in test diet animals. Another small-scale investigation compared ground corn with whole-grain rice diets, concluding that the more fibrous latter diet was associated with greater muscular development of the gizzard and prevention of cecal colonization two days after a modest (10^3 cfu) oral challenge with *C. jejuni* at 30 days of age (Nishii, Yasutomi, & Sone, 2015).

Litter and other environmental treatments

There have been two reports on the commercial-scale use of litter treatments with chemical acidifiers in an attempt to control the intensity of *Campylobacter* contamination of the environment and external surfaces of birds, and possibly reduce its spread among birds also. Pope and Cherry (2000) examined one rearing cycle in paired test and control houses on 12 farms, where a sodium bisulfate-based product was applied mechanically at the manufacturer’s recommended rate to litter that had been carried-over between a (variable) number of consecutive flocks. A treatment was applied shortly before the litter

774 was in use by the experimental flock, and again one week before slaughter. Environmental samples
775 and carcass rinses of specimen birds, performed shortly before de-stocking and on the slaughter line,
776 showed no significant differences between test and control flocks with respect to *Campylobacter*
777 contamination. The pH and ammonia control effects of the litter treatment proved significant but were
778 short-lived and, although reductions in numbers of *E. coli* and *Salmonella* were found on carcasses
779 from test flocks, these were not statistically significant. The other study involved application of
780 acidifier (sodium bisulfate or aluminum sulfate) over one cycle on 10 farms (Line & Bailey, 2006).
781 The age/re-use status of the litter in treated houses was not specified. Feces samples were monitored
782 weekly. Use of acidifier was associated with a potentially-useful delay in the onset of *Campylobacter*
783 shedding, more so with the sodium than the aluminum salt. However, using this intervention alone,
784 differences between test and control houses were not evident by six weeks of age, nor was there any
785 difference in *Campylobacter* counts from on-farm carcass rinses at slaughter age.

786

787 Orhan et al. (2017) reported lower ammonia concentrations, litter treatments, and increased air
788 temperature to be all associated with lower or zero *Campylobacter* prevalence in a risk factor study of
789 53 poultry houses in the USA. Commercial trials by a major UK supplier using biomass heating to
790 reduce humidity in poultry houses have been described as significantly reducing the proportion of
791 *Campylobacter*-positive flocks (Wearne, 2015), but detailed reports are lacking at present.

792

793 **Bacteriocins**

794 Bacteriocins are low-molecular-weight bacterial peptides that have antibacterial properties, involving
795 pore-forming actions, and with highly variable spectra of activity. Given their ubiquity in
796 microbiological communities, their specificity for prokaryotes, their susceptibility to degradation, and
797 an apparent lack of cross-resistance among bacteriocins or with antibiotics, they are attractive
798 candidates for targeted suppression of zoonotic pathogens in food and livestock. Screening for bacteria

799 with inhibitory effects on *Campylobacter* isolates has identified producers of several potentially useful
800 bacteriocins, as reviewed by Svetoch and Stern (2010).

801

802 Effects of two thermostable candidate bacteriocins (E-760 and E 50-52), with activity against a wide
803 range of *Campylobacter* strains, have been examined in naturally colonized and commercially raised
804 birds at slaughter age. In one study, there was a reduction in shedding of *Campylobacter* from between
805 10^4 and 10^7 cfu/g feces to undetectable numbers in nine of 10 birds fed bacteriocin E-760 for four days
806 (Line et al., 2008). In the other study, bacteriocin E 50-52 was supplied to 30 mature broilers in
807 drinking water and was associated with a five $\log_{10}$ unit or more reduction in *C. jejuni* counts in cecal
808 homogenates, to between 10^2 and 10^3 cfu/g cecal content, after a one- to three-day exposure (Svetoch
809 et al., 2008). However, promising as these studies are, there has been a lack of follow-up reports,
810 including any larger-scale trials.

811

812 **Bacteriophages**

813 For bacteriophages, the mode of control necessarily requires *Campylobacter* organisms to be present
814 above the phage proliferation threshold for phage activity and multiplication, therefore the control
815 strategy has focused on reducing numbers of *Campylobacter* cells in advance of slaughter rather than
816 preventing colonization. Important factors in the outcome of phage applications include the activity
817 spectrum of the lytic phage or phage mix employed, the timing of application, and the ratio of phage-
818 to-*Campylobacter* numbers (multiple of infection) in the intestine (Grant, Hashem, & Parveen, 2016).
819 A longitudinal study, following introduction of a lytic bacteriophage cocktail into experimental flocks
820 (Kittler, Fischer, Abdulmawjood, Glünder, & Klein, 2014), demonstrated that both phage-susceptible
821 and non-susceptible strains of *C. jejuni* persisted and spread amongst the birds, indicating that long-
822 term control via bacteriophages is likely to be negligible. The development of resistance to a
823 bacteriophage strain is commonly observed even in the short-term (Grant et al., 2016), but

824 *Campylobacter* genomic instability, co-evolution of host and phage, and fitness costs may limit the
825 significance of this (Carvalho et al., 2010; El-Shibiny et al., 2009; Loc Carrillo et al., 2005; Scott et
826 al., 2007).

827

828 Loc Carillo *et al.* (2005) administered one of two phages, with antacid (calcium carbonate), to small
829 numbers of 25-day-old birds around a week after challenge with a matched phage-susceptible *C. jejuni*
830 strain. Daily *post mortem* examinations revealed persistence of the phage in the cecum for all of the
831 five-day follow-up, provided the host *Campylobacter* was present. A maximum 3.5 to four log₁₀ unit
832 reduction in *Campylobacter* density was observed, at one to three days post-phage administration, but
833 the detail of the timing and degree of peak effect varied between phage doses, phage strain, and
834 phage/host combination. *In vitro* data on speed of action and optimal host/phage ratio did not correlate
835 closely with the *in vivo* observations.

836

837 Another small-scale trial (Wagenaar, Bergen, Mueller, Wassenaar, & Carlton, 2005) used a single
838 phage given around or after challenge at 10 days of age with a susceptible *C. jejuni* strain. An extended
839 (four-week) reduction, of around one log₁₀ unit, in counts of cecal *C. jejuni* was observed. A mix of
840 two phages, given to older (six- to seven-week-old) *C. jejuni*-challenged birds, reduced cecal counts
841 to a similar degree for a three-week follow-up period.

842

843 El-Shibiny *et al.* (2009) investigated the effect of a broad-host-range phage against both *C. jejuni* and
844 *C. coli* in small numbers of birds colonized by challenge at 20 days old. Given with antacid at 25 days,
845 at doses spanning 10⁵ to 10⁹ plaque-forming units (pfu), the phage was associated with a rapid peak of
846 *C. jejuni* suppression in the cecum (24 hr, two log₁₀ units) at 10⁷-10⁹ pfu and above, but had a slower
847 peak effect on *C. coli* (48 hr, two log₁₀ units), and only at the highest dose of 10⁹ pfu. It was

848 hypothesized that poor colonization of the small intestine by the *C. coli* strain may have delayed the
849 onset of phage replication cycles for this species.

850

851 A small-scale trial of bacteriophage effect was conducted by Carvalho *et al.* (2010) using a cocktail of
852 three phages with complementary lytic spectra. They were given orally (10^6 pfu per bird in a buffer
853 solution or 1.5×10^7 pfu per bird in feed) with calcium carbonate to small groups of week-old chicks
854 that had been inoculated at day-old with *C. jejuni* or *C. coli*. Bacteriophage titers on cloacal swabs
855 were substantial throughout the subsequent days of the experiment, indicating phage replication, and
856 the geometric means of *Campylobacter* counts in feces were significantly (1.4 to 2.1 $\log_{10}$ units) lower
857 in phage-inoculated birds compared with controls, from four days post-administration until the end of
858 the experiment three days later. Comparisons were made of phage resistance among *Campylobacter*
859 isolates from experimental birds; resistance increased from 6 to 13% of isolates following exposure to
860 bacteriophages, but many of these reverted to sensitivity following re-passage through chicks.
861 Therefore, phage resistance might not be a major issue for commercial application of the technology.

862

863 Hammerl *et al.* (2014) investigated single versus combined versus sequential dosing, with phages taken
864 from typing groups II and III. Small numbers of chickens were given a colonizing, phage-sensitive
865 *C. jejuni* strain at 20 days of age; they were then dosed with antacid plus 10^8 - 10^{10} pfu phage seven
866 days later (or twice, seven, and eight days later), and then were monitored by feces samples before
867 *post mortem* examination four days after phage administration. Counts of *Campylobacter* in feces were
868 reduced, with peak suppression at 72 hours post-dosing, among birds inoculated with a single group
869 III phage (greater than one $\log_{10}$ unit reduction) and with two sequential phages from groups III then
870 II (three $\log_{10}$ units reduction). However, no significant reduction was seen with a mix of two group
871 III phages administered simultaneously. This was despite one of the phages being associated with a

greater than one log₁₀ unit suppression when given alone, and lytic activity of the phage mix being observed *in vitro*.

A field trial of a bacteriophage intervention was reported by Kittler *et al.* (2013), using a mix of four lytic typing phages in drinking water (5.8 to 6.5 log₁₀ units pfu per bird as a one-time dose) with flocks that were naturally colonized by *Campylobacter* and at a late stage of rearing (31 to 36 days of age). Periodic feces samples were examined post-dosing, and cecal samples were taken at slaughter. Results from three trials, using paired intervention and control flocks on two farms, varied substantially. The first trial showed a significant (three log₁₀ units) reduction in shed *Campylobacter* in dosed birds, that was sustained until slaughter six days later, at which time phages were re-isolated from birds. However, the second trial showed a brief shedding of phages only and no significant difference between intervention and control flocks, whilst in the third trial the control flock also became infected with the bacteriophages and a difference in *Campylobacter* shedding was not seen between the flocks, nor was any consistent overall reduction in *Campylobacter* counts seen over time in either flock.

Probiotics

There is evidence that an absent or altered intestinal microflora permits more intense colonization of the chicken gut (and other tissues) by *C. jejuni*, at least in the short-term (Z. Han et al., 2017). Probiotics have been evaluated in attempts to both exclude and suppress colonization of birds. One probiotic that has been examined under commercial conditions is a licensed preparation of *Bacillus subtilis* spores ('Calsporin', 10¹⁰ cfu/g), which is thought to exert effects in the intestine, when continuously fed, by altering the balance of the existing microflora, particularly *Lactobacillus* spp., as *B. subtilis* is not itself a gut commensal organism. Being in spore form, the preparation has the considerable potential advantage of being robust in the face of normal feed manufacturing processes.

897 One study, conducted by the manufacturer, used Calsporin in feed with birds from 17 or 34 days of
898 age in two commercial rearing houses (Maruta et al., 1996). Small pools of fecal droppings were
899 collected at 56 days of age. Compared with a control house, test houses had a significant (2 to 2.5 log₁₀
900 units) reduction in mean *Campylobacter* counts, and in the proportion of positive fecal pools (16% to
901 40% versus 100%). There was, in an allied but separate experiment, a modest reduction in the counts
902 and frequency of naturally acquired *Salmonella* in feces. Two later trials each used 2400 test and 1200
903 control birds in an experimental facility, feed-amended with Calsporin from one-day-old, and with
904 natural colonization by *Campylobacter* (Fritts et al., 2000). Cultures of pre-chill carcass rinses from
905 96 birds per trial revealed a modest yet significant reduction in mean *Campylobacter* counts from test
906 birds in the first, but not the second, trial (2.85 versus 3.43 log₁₀ units cfu/mL) and in combined data
907 from both trials (3.05 versus 3.26 log₁₀ units cfu/mL). A significant reduction in the prevalence of
908 *Salmonella*-positive carcasses was also seen.

909

910 A recent commercial field trial (Smialek, Burchardt, & Koncicki, 2018) of a lactic acid bacteria (LAB)
911 and yeast product ('Lavipan') at 0.05% incorporation, throughout rearing in a single 18,000-bird flock,
912 showed significantly lower counts of *Campylobacter* in droppings at the end of rearing, compared with
913 a contemporaneous control flock and with control flocks in the same house and other houses before
914 and after the trial. Taking into account observed variation between flocks in the test and non-test
915 houses, the reduction in counts of droppings associated with the probiotic product was around two
916 log₁₀ units. At slaughter, lower (one log₁₀ unit) cecal counts were also observed in comparison with
917 the contemporaneous flock; this did not achieve formal statistical significance as sample sizes were
918 small.

919

920 A small-scale trial, conducted in a study described above under acid treatment of feed (Guyard-
921 Nicodème et al., 2016), included Calsporin as a probiotic feed treatment throughout rearing and

922 reported a significant ($1.7 \log_{10}$ units) reduction in cecal *Campylobacter* colonization at slaughter age,
923 four weeks post-challenge. This effect was seen on a single-trial experiment in the context of wide
924 variation between individuals, and was not observed at earlier time points. However, a similar study,
925 using a mix of multispecies probiotic and a prebiotic fed throughout rearing, also reported a reduction
926 (average $1.5 \log_{10}$ units) in cecal *Campylobacter* only at the final sampling, four weeks after challenge
927 (Millán, Puentes, Guyard, Tenk, & Medel, 2015). It may be that some products do indeed have a
928 delayed suppressive effect (also reported below with a probiotic-containing ‘synbiotic’ product),
929 although evidence is at present fragmentary.

930

931 Another small-scale trial used a commercial probiotic mix of *Enterococcus*, *Pediococcus*,
932 *Bifidobacterium*, and *Lactobacillus* (‘PoultryStar sol’) given daily from one-day-old at a rate of either
933 2 or 20 mg per bird in drinking water (Ghareeb et al., 2012). Chicks were challenged from day one
934 with *C. jejuni*, either by oral administration (10^4 cfu) or via contact with previously inoculated seeder
935 birds that were shedding the bacterium. When birds were examined *post mortem* a substantial and
936 significant reduction in cecal *Campylobacter* spp. counts was found: greater than six $\log_{10}$ units for
937 seeder-exposed birds and three to five $\log_{10}$ units for directly inoculated birds, albeit in a study
938 terminated well before slaughter age, at 15 days post-challenge. By contrast, a single-strain probiotic
939 (*Enterococcus faecalis*, shown to have bacteriocin-mediated anti-*Campylobacter* activity *in vitro* and
940 given at 10^4 or 10^8 cfu daily from one-day-old) had no effect on *C. jejuni* colonization a week after
941 seeder bird challenge from 15 days old (Robyn, Rasschaert, Hermans, Pasmans, & Heyndrickx,
942 2013a). In this study the probiotic strain was found in the cecum at densities of 10^4 to 10^5 cfu/g.

943

944 Aho *et al.* (1992) reported trials on a small commercial scale (1,800 birds in 60-bird groups) of a
945 competitive-exclusion (CE) mix combining a commercial product (‘Broilact’) and mucin-colonizing
946 *Campylobacter*-like organisms termed K-bacteria. Initial trials showed that a combination of K-

947 bacteria plus facultative anaerobic bacteria (present in Broilact) was associated with suppression of
948 *Campylobacter* colonization. The full-scale trial showed a difference in mean cecal *C. jejuni* between
949 test and control birds of between one and two log₁₀ units at slaughter after transport, albeit with much
950 individual variation, following exposure to the CE mix in water for eight hours, before introduction of
951 *C. jejuni* seeder birds at four or 18 days of age. In the birds challenged at 4 days of age a delay in
952 detectable cecal colonization was also seen. It was hypothesized that exclusion of *Campylobacter* may
953 have occurred following occupation of mucin sites by K-bacteria plus iron utilization by the Broilact
954 flora. Larger-scale field trials were anticipated by the authors, but have not been reported.

955

956 In a 280-bird study, two- or four-strain mixes of *Lactobacillus* spp. were associated with significantly
957 lower cecal counts (0.5 log₁₀ units and greater, depending on strain mix) of *Campylobacter* when given
958 at 10⁹ cfu/kg feed in the last week before slaughter to birds naturally colonized with *C. jejuni* (Cean et
959 al., 2015). By comparison, feeding the same probiotic mixes from the beginning of life neither
960 prevented colonization nor enhanced suppression of *Campylobacter* at slaughter.

961

962 **Prebiotics**

963 There has been some interest in the use of prebiotic substances (aiming to manipulate intestinal
964 microbiota, typically by supplying fermentable substrates) in *Campylobacter* control, but no field trials
965 have been reported. Mannose-based sugars and oligosaccharides may also, or alternatively, have
966 effects on bacterial adhesion and be immunomodulatory. A small-scale trial used β-1,4 mannobiose at
967 130 ppm in broiler feed from one-day-old (Y. Han, 2009). Birds were progressively removed from 15-
968 bird pens, for *post mortem* examination of cecal contents at 14, 21, 28 and 41 days of age. The origin
969 of the *Campylobacter* in this study (natural versus experimental inoculation) is unclear. The
970 intervention diet was associated with lower *Campylobacter* counts than a control diet at 21, 28, and 41
971 days, which on the last occasion was statistically significant, at 1.65 log₁₀ units. Another study used a

972 commercial mix of mannan oligosaccharide, mannose, and glucose ('BioMOS') in the feed of 55-bird
973 pens throughout rearing, comparing this with groups having in-feed antibacterial agents (virginiamycin
974 or bacitracin) and untreated controls (Baurhoo, Ferket, & Zhao, 2009). No consistent effect of any
975 treatment was seen, either upon the onset of *Campylobacter* shedding or of cecal counts at six weeks
976 of age.

977

978 **Miscellaneous products**

979 A non-significant reduction in cecal *C. jejuni* counts (around 2 log₁₀ units but with wide individual
980 variation) was observed among 39-day-old broilers that had been orally challenged at one day of age
981 and subsequently given a daily dose in feed of a 'synbiotic' additive, of lipid-encapsulated
982 *Bifidobacterium longum* plus an oligosaccharide (Baffoni et al., 2017). Cecal counts earlier in life were
983 similar to controls. Of six feed or water treatments (probiotic, prebiotic, plant extract, clay, and/or
984 organic acid blend) administered to long-cycle free-range broilers experiencing natural colonization at
985 five to six weeks of age, only one (combination clay product in feed plus organic acid in water, given
986 during the last week of life) was associated with a significant but small reduction in cecal and skin
987 *Campylobacter* counts at slaughter (Guyard-Nicodème et al., 2017).

988

989 In a small-scale study, already described under acid treatment of feed (Guyard-Nicodème et al., 2016),
990 a yeast plus growth media prebiotic-like product (XPC) was tried in feed throughout rear and
991 reportedly associated with a significant (average three log₁₀ units) reduction in cecal *Campylobacter*
992 concentration, but only by around four weeks post-challenge. A similar study using a mix of XPC and
993 probiotic (Millán et al., 2015) was similarly associated with a delayed reduction in *Campylobacter*
994 counts, as already described.

995

996 A diet high in fermentable non-starch polysaccharides, with or without degrading enzymes to improve
997 digestive capacity and increase prebiotic oligosaccharide yield, was tested by Molnár *et al.* (2015) in
998 a small-scale study with heavy *C. jejuni* challenge (10^8 cfu) at two weeks of age. The diet with high
999 non-starch polysaccharides plus enzymes was associated with substantially lower (around four $\log_{10}$
1000 units) *Campylobacter* counts in the jejunum and cecum. However, the phenomenon was transient, with
1001 no significant differences compared with controls by three weeks post-challenge, despite persisting
1002 differences in hindgut pH and SCFA content.

1003

1004 A small number of compounds inhibitory to the bacterial twin-arginine translocation pathway, with
1005 low eukaryote toxicity and other suitable characteristics, have been identified. These were associated
1006 with a reduction in broiler cecal *Campylobacter* concentration of up to 1.2 $\log_{10}$ units in an exploratory
1007 study (Deblais *et al.*, 2017). The bacterial twin-arginine translocation pathway is important for
1008 *Campylobacter* colonization of the chicken intestine and there appears to be no mammalian or avian
1009 homolog (Kassem, Zhang, & Rajashekara, 2011), thus making it an attractive target.

1010

1011 **Vaccination**

1012 Vaccination trials have thus far been limited to small-scale studies. Findings have been variable,
1013 although promising results have been reported in some recent cases (Meunier, Guyard-Nicodème,
1014 Dory, & Chemaly, 2016; Meunier *et al.*, 2017). There is reasonable evidence that poultry can exert
1015 immunological control over *Campylobacter* colonization, from natural clearance of colonization or of
1016 strains in long-lived flocks, plus protective effects of prior exposure to *Campylobacter* spp.,
1017 examination of specific immune responses, and effects of immunosuppression (Colles *et al.*, 2015; de
1018 Zoete *et al.*, 2007; S. Humphrey *et al.*, 2014; Vaezrad *et al.*, 2017). The phenotypic variation seen
1019 among *Campylobacter* strains, plus differences between mammalian and avian immunity with respect

1020 to innate and anamnestic responses, have contributed to the challenge of selecting suitable vaccine
1021 antigens (de Zoete et al., 2007).

1022

1023 Substantial control over colonization (reductions in cecal count of between two and six log₁₀ units)
1024 following *C. jejuni* challenge has been reported using injected crude or defined (CjaA, FlpA, FlaA)
1025 preparations of *Campylobacter* outer membrane proteins (Annamalai et al., 2013; Buckley et al., 2010;
1026 Neal-McKinney et al., 2014). However, other such proteins have not been associated with significant
1027 or sustained protection when similarly tried as vaccines (Chintoan-Uta, Cassady-Cain, & Stevens,
1028 2016; Neal-McKinney et al., 2014), and the reductions in colonization associated with injected CjaA
1029 have been significant in one study (Buckley et al., 2010) but insignificant in another (Chintoan-Uta et
1030 al., 2016). A recent small trial used *Campylobacter* capsular polysaccharide conjugated with diphtheria
1031 toxoid and injected with adjuvant (Hodgins et al., 2015). Following oral challenge, modestly (mean
1032 0.64 log₁₀ units) lower cecal *C. jejuni* counts were observed nine days later in vaccinated birds.
1033 Considerably more marked control of colonization has recently been reported using an N-linked
1034 glycoprotein surface molecule preserved across all tested *C. jejuni* and *C. coli* strains, alongside
1035 evidence of an effect of challenge dose on vaccine efficacy (Nothaft et al., 2016).

1036

1037 For use in broiler chicks, a vaccine suitable for mass oral or mucosal delivery is highly desirable, and
1038 much recent effort has been focused in this area. The genomic and phenotypic instability of
1039 *Campylobacter* makes it an unsuitable live vaccine platform, so workers have concentrated on subunit
1040 vaccines, typically using *Salmonella enterica* as a vector. Notable findings were reported by
1041 Wyszynska et al. (2004), who introduced the gene encoding CjaA (a solute-binding element of a
1042 cysteine transporter system that is well-preserved between strains) into an already-licensed *Salmonella*
1043 Typhimurium avian live vaccine strain. Chicks immunized orally twice in the first fortnight of life
1044 with the experimental vaccine proved strongly resistant to colonization with a field strain of *C. jejuni*

1045 following high-level challenge two weeks later, with only three of 20 vaccinated birds being cecal
1046 culture-positive, and these few having around six $\log_{10}$ units lower density compared with the
1047 uniformly-colonized controls. However, this degree of protection has not been reproduced using the
1048 same vector and challenge strains in a different line of birds (Buckley et al., 2010), nor using differently
1049 engineered *Salmonella* vector strains (Buckley et al., 2010; Łaniewski et al., 2013), thus emphasizing
1050 the difficulty of generating consistent protection in the face of variable host, vaccine, and challenge
1051 strain factors.

1052

1053 There are, nonetheless, several promising antigens identified for subunit vaccines, including CjaA,
1054 CjaD, and Peb1A, which might be used in combination. Furthermore, Nothaft et al. (2016) have
1055 recently described the successful surface expression of N-linked *C. jejuni* glycoprotein by an
1056 engineered *E. coli* strain, yielding substantial (six to eight $\log_{10}$ units) reductions in cecal colonization
1057 in a small-scale study after oral vaccination at seven and 21 days followed by oral challenge at 28 days.
1058 An alternative approach for antigen delivery that shows some promise is the use of the coccidian
1059 parasite *Eimeria tenella* as an attenuated, immunogenic, and highly host-specific delivery vector
1060 (Clark et al., 2012).

1061

1062 Fortunately, live vaccination protocols that start very early in life appear to be as effective as delayed
1063 dosing (Buckley et al., 2010; Layton et al., 2011), which has practical commercial benefits. Indeed, *in*
1064 *ovo* vaccination with a subunit CjaA+D preparation mounted in liposomes has proven to be protective,
1065 reducing post-challenge cecal counts by up to two $\log_{10}$ units, in a recent small-scale trial (Kobierecka
1066 et al., 2016).

1067

1068 **Genetic resistance**

1069 Certain breeds of broiler chickens are less likely than others to be colonized to a high level by
1070 *Campylobacter* (Georgiev et al., 2017), and there is evidence that it is possible to selectively breed for
1071 resistance to colonization, altering *Campylobacter* density in affected birds by two log₁₀ units or more
1072 (EFSA, 2011). Studies using inbred resistant chickens have identified several candidate genetic loci,
1073 including those involving function or structure of: chemokines, cadherins, innate immunity, and the
1074 major histocompatibility complex (Psifidi et al., 2016). Along with responses to some recent candidate
1075 vaccines, this diminishes the view of *Campylobacter* colonization as a passive, purely commensal
1076 interaction, and raises the attractive possibility that genetic manipulation of colonization determinants
1077 may also elevate resistance to other infectious pathogens. Recent findings suggest that the potential
1078 for genetic control over the degree of *Campylobacter* colonization among commercial broilers is likely
1079 to be limited, albeit compatible with continued high production (Bailey et al., 2018).

1080

1081 **Ambient temperature**

1082 It may be that heat stress contributes to the seasonal peak in incidence seen in cooler temperate regions,
1083 especially if the housing designs struggle to maintain adequate ventilation to older flocks in the hottest
1084 days of the year. Furthermore, there may be an indirect effect of heat stress via reduced biosecurity,
1085 caused by producers wearing less protective clothing and opening doors, windows, and so forth, to
1086 increase ventilation during hot weather in temperate climates.

1087

1088 Small-scale trials mimicking cyclical heat stress (generally 31 °C and above) on birds in the later stages
1089 of rearing have demonstrated reduced production performance accompanied by elevated
1090 corticosterone plus immunosuppressive phenomena (Al-Ghamdi, 2008; Campos et al., 2016; Lara &
1091 Rostagno, 2013; Park et al., 2013; Quinteiro-Filho et al., 2010, 2012; Rimoldi et al., 2015; Verbrugghe
1092 et al., 2012). Effects of heat stress on the gut, in particular, are indicated by evidence of mild enteritis

1093 (Quinteiro-Filho et al., 2010, 2012) and altered intestinal morphology in experimentally stressed birds
1094 (Burkholder, Thompson, Einstein, Applegate, & Patterson, 2008; Lara & Rostagno, 2013).

1095

1096 Alterations in the gut microbiota (Burkholder et al., 2008), including elevated counts of *Salmonella*
1097 and *E. coli* but depressed *Lactobacillus* (Park et al., 2013), suggest a shift in favor of enteropathogens
1098 among heat-stressed birds. There is, however, little reported work on the effects of heat stress upon
1099 *Campylobacter* colonization, beyond pertinent observations that catecholamine stress hormones
1100 (adrenaline/epinephrine and noradrenaline) have effects on patterns of *C. jejuni* gene expression
1101 resulting in increased growth, invasiveness *in vitro*, and motility plus altered virulence gene regulation
1102 and expression (Verbrugghe et al., 2012; Xu et al., 2015).

1103

1104 ***A British perspective on commercial-scale Campylobacter control***

1105 Expert opinion was solicited by the UK Food Standards Agency for consideration of the situation in
1106 the UK, in the context of measures adopted elsewhere (FSA, 2010a). At pre-harvest stages, the
1107 desirability of improved biosecurity faced challenges around the preponderance of older wooden
1108 houses in the UK industry. The feasibility and benefits of intensive fly control, as demonstrated in
1109 Denmark and elsewhere, were considered to be uncertain. Given the open market into the UK and
1110 consumer preference for fresh meat, it was unclear how the costs of improved control at the producer
1111 level might be borne without loss of market share to imported chicken, perhaps with poorer control of
1112 *Campylobacter*. In this regard, the effects of international trade in poultry meat were included in a
1113 recent modeling analysis (van Wagenberg, van Horne, Sommer, & Nauta, 2016). It examined the costs
1114 and benefits of certain (mostly biosecurity-related) evidence-supported interventions, and illustrated
1115 marked variations in projected cost-effectiveness for reducing human disease burden, both between
1116 interventions and between EU countries.

1117

1118 However, more recent concerted actions by the Food Standards Agency, including publication of
1119 *Campylobacter* contamination data from major retailers, appears to have transformed the climate for
1120 the adoption of incentive schemes and for innovation in producer practices in the UK. Progress has
1121 been driven by a renewed strategy (Wearne, 2013), born out of a failure to achieve targets established
1122 by a joint government and industry initiative (FSA, 2010b), to reduce heavily contaminated carcasses
1123 to less than 10% by 2015. There has been a subsequent move to implement more targeted, risk-based,
1124 and proportionate official controls, plus transparent industry sampling and publishing of contamination
1125 data, aimed at achieving a demonstrable effect on public health (Wearne, 2016).

1126

1127 In addition to various research projects, action on farms has been publicly pledged by major producers
1128 and retailers. These include: the enhancement of hygiene barriers (including double barriers),
1129 improved training for producers, external auditing, and the adoption of no-thinning policies,
1130 particularly for flocks supplying the fresh whole-bird market (2 Sisters Food Group, 2015; Moy Park,
1131 2015; Whitworth, 2015). Furthermore, some incentive schemes for producers using biosecurity
1132 measures, or even *Campylobacter*-free flocks, as outcomes have been introduced by major retailers
1133 and suppliers (Wearne, 2015; Whitworth, 2015). The most powerful incentive for what appears to be
1134 recent progress against the 2010 target for retail carcasses is, in the opinion of the Food Standards
1135 Agency, the adoption from 2014/15 of quarterly publications of *Campylobacter* contamination data
1136 from non-anonymized retail surveys among the major retailers (Wearne, 2015). There has been a
1137 steady reduction in the proportion of heavily-contaminated carcasses among large retailers in the
1138 quarterly surveys, albeit principally achieved at post-production stages and possibly achieved in part
1139 by the removal of neck skin from carcasses before they are sent to retail, where sampling is done (FSA,
1140 2016). Government agency testing has more recently focused on smaller establishments, where there
1141 appears to have been less progress (FSA, 2017).

1142

1143 **Summary**

1144 Biosecurity and hygiene measures clearly have a strong role in preventing flock colonization in the
1145 field, but there is plentiful evidence that such measures are often poorly implemented. Risk factor
1146 analyses have identified older broiler houses as posing a heightened risk of *Campylobacter* incursion
1147 with, potentially, a number of factors involved including: difficulties with C&D, challenges to hygienic
1148 access by personnel, ventilation systems, wildlife access, and drinker systems. Recent work also
1149 suggests that *Campylobacter* may commonly be present in houses before flock placement, sometimes
1150 at levels undetectable by conventional sampling and culture techniques.

1151
1152 Perhaps because of the ease with which a lapse in biosecurity may result in flock colonization, some
1153 biosecurity and hygiene field intervention studies fail to show protective effects of enhanced
1154 procedures. Efforts to rear flocks that are not colonized by the time of depopulation may also be
1155 counteracted by *Campylobacter* contamination introduced by catching crews during partial
1156 depopulation, catching equipment that has to be driven into occupied poultry houses, and/or transport
1157 crates, all these being factors that are not readily influenced by individual farm management.
1158 Nonetheless, negative attitudes among farm managers about the value of biosecurity was identified by
1159 thinning crews, along with concerns about the physical challenges and work-rate required of operatives
1160 (Millman et al., 2017).

1161
1162 Where ‘clean’ birds are contaminated by catching crews or by transport crates, the level of colonization
1163 by the time of slaughter probably depends on the conditions and duration of transport and lairage. In
1164 the longer term, when the prevalence of flock colonization is substantially reduced, then residual
1165 contamination of crates may be less frequent. Contamination of crates and of thinning equipment and
1166 personnel should also be considered to pose a risk for birds remaining on-farm after thinning.

1167

1168 Clearly, there is a major issue relating to compliance among operators. There appears to be a relentless
1169 tendency in human medicine and animal production for hygiene observance to decline over time,
1170 requiring constant reinforcement and training. The various recent studies of Racicot et al. (2011, 2012a,
1171 2012b) regarding hygiene procedures when entering and leaving poultry houses indicate that levels of
1172 general compliance can be very low, especially among non-managerial and non-supervisory
1173 employees. Training programs seem more likely to be effective when they take into consideration the
1174 educational level of a work-force, using multi-lingual approaches with a target audience of non-native
1175 speakers, and do not pre-suppose a secure understanding of the nature of infectious agents.

1176
1177 Some evidence suggests that absolute prevention of flock colonization may require that no bird
1178 encounters a colonizing dose of *Campylobacter* during rearing as, thereafter, multiplication and
1179 shedding appears to occur at an intensity that overwhelms suppressive treatments. To satisfy this
1180 exacting requirement, barriers to exposure (hygiene and biosecurity) can be augmented by flock
1181 treatments that raise the threshold for colonization via oral exposure (Table 1). Inclusion of organic
1182 acids in feed or drinking water (the latter route potentially also providing a convenient mode of water
1183 sanitization) appears, based on present evidence of mainly small-scale trials, to hold out the prospect
1184 of usefully raising colonizing thresholds, although the reports of field trials do not show consistent
1185 efficacy. Alternatively, non-acid water treatments may act simply as a water hygiene measure, without
1186 *in vivo* effects on the colonizing threshold dose of *Campylobacter*. In this respect they may be regarded
1187 essentially as part of the hygiene armory but, like other elements in this category, it cannot be assumed,
1188 without monitoring, that they are being implemented effectively.

1189
1190 There is also some evidence for the importance of environmental load in transmission, as suggested
1191 by risk analyses where lower commercial flock *Campylobacter* colonization has been associated either
1192 with sanitised drinking water (Torralbo et al., 2014) or with the use of non-reservoir drinkers (Høg et
1193 al., 2016). Some of the other cited studies, concerning water and litter treatment, provide further

1194 support for this view. Such effects may reduce contamination pressure at slaughter. The potential role
1195 of reduced transmission in intra-flock prevalence is further highlighted in work suggesting that it is
1196 lower transmissibility between younger birds, rather than resistance to colonization, which determines
1197 the lag phase before flock-wide spread of *Campylobacter* (Conlan et al., 2011).

1198

1199 Trials of biological control agents, using either probiotics or bacteriophages, show variation in
1200 protocols and outcomes, similar to treatment using antimicrobial agents. Results from small-scale
1201 probiotic trials, with direct or seeder bird challenge, show promise but also inconsistencies. Field trials
1202 with *B. subtilis*, and with lactic acid bacteria plus yeast probiotics, have failed to prevent flock
1203 colonization but were associated with potentially useful reductions in the intensity of colonization and
1204 shedding. Factors that may determine successful suppression of *Campylobacter* (bacterial species,
1205 dose quantity and frequency, and timing relative to exposure) remain largely unknown. Alternatively,
1206 attempts to manipulate the intestinal environment and microflora via the constituents and structure of
1207 the diet suggest that some measure of control can be achieved by this approach, although any effects
1208 on production efficiency remain to be explored.

1209

1210 Short-term interventions applied at the end of rearing may suppress the number of *Campylobacter*
1211 organisms being shed or carried in the intestine at the time of slaughter. Of these, certain bacteriocins
1212 have been associated with the most dramatic reductions of *Campylobacter* in naturally colonized birds,
1213 but field-scale trials are not yet reported. Efficacy in this mode of use at large scale has been seen with
1214 bacteriophages, but this appears to require considerable refinement and further work if it is to be
1215 reliable. Acid additives for water also show potential in this respect and have been tried in the field,
1216 but once again results have been inconsistent.

1217

1218 Some trials have sought to suppress (not prevent) *Campylobacter* colonization throughout an entire
1219 rearing cycle, for example *B. subtilis* spores or a mannose-based prebiotic. Results have indicated there

1220 may be significant reduction of cecal and/or carcass counts associated with these. However, some
1221 results are inconsistent between trials, and the costs of using such products for most or all of each
1222 production cycle (compared with suppressive treatments targeted at the end of rearing) may outweigh
1223 what appear to be quite modest beneficial effects.

1224

1225 Several interventions using anti-*Campylobacter* agents, such as bacteriocin or probiotics, have
1226 appeared to show promising efficacy, but then follow-up field trials have not been reported. Among
1227 published trials there is ample evidence that inconsistent results bedevil investigations of
1228 *Campylobacter* control methods, so it may be that less impressive larger-scale results are not
1229 published. In this regard, notable features of reported comparative trials of additive products include:
1230 wide variation of cecal *Campylobacter* counts among both test and control birds, unpredictable
1231 patterns of apparently efficacious versus ineffective products, and significant reductions in
1232 *Campylobacter* colonization only after several weeks' use of certain products. Marked variation may
1233 also be seen in *Campylobacter* counts between successive flocks subjected to the same treatment
1234 (Smialek et al., 2018). When such major variation is seen, even within such study groups using similar
1235 protocols, it is not surprising that a coherent picture of efficacy does not emerge from non-linked
1236 studies (Meunier et al., 2016). The effects of host, gut microbiota, *Campylobacter* strain, and
1237 phenomena such as cyclical variation in colonization upon the outcome of trials remain incompletely
1238 understood.

1239

1240 The potential for vaccination to induce effective control of *Campylobacter*, even in the immature birds,
1241 has been demonstrated. The effects of host and *Campylobacter* strain variation, in addition to choice
1242 and presentation of antigen, remain as obstacles to consistent and predictable vaccine protection
1243 against high-level colonization, but progress is encouraging. Approaches to increasing flock resistance

1244 to *Campylobacter* colonization by manipulating bird genetics or the environmental conditions for
1245 housed broilers may hold potential but remain largely unexplored.

1246

1247 There is a need for large-scale field studies to provide robust evidence of the efficacy of specific
1248 interventions, in order to direct actions taken by the broiler industry. This is especially true of measures
1249 aimed at preventing the establishment of flock colonization through low numbers of *Campylobacter*
1250 organisms that are able to bypass biosecurity procedures. Using the established principles of
1251 standardization (as applied to medical clinical trials) across multiple broiler holdings in different
1252 companies and/or countries is likely to be more useful than the present alternative of attempting to
1253 gain evidence from small and often poorly controlled trials carried out using differing methodologies
1254 (Blajman et al., 2014).

1255

1256 **Conclusions**

1257 Given the apparently intractable nature of the problem, practical control of *Campylobacter* at present
1258 probably requires the adoption of multiple measures built upon a foundation of excellent biosecurity
1259 and hygiene, which has allied benefits in controlling and excluding other bird and zoonotic pathogens,
1260 such as *Salmonella*. Studies on biosecurity and hygiene measures have highlighted the existence of
1261 major challenges to their effective and consistent implementation in the context of commercial broiler
1262 production. Nonetheless, improved control of *Campylobacter* has been observed when biosecurity is
1263 enhanced by various interventions, measured as delay or prevention of flock colonization, or a
1264 reduction in intensity of shedding. Measures complementary to biosecurity and hygiene retain promise,
1265 but trials are inconsistent and often small-scale (Table 1). There has been demonstrable progress
1266 recently, in the UK and elsewhere, on reducing the prevalence of heavily contaminated retail meat
1267 through improved slaughter hygiene measures, but keeping flocks *Campylobacter*-free up to the point
1268 of slaughter remains an elusive goal.

1269

1270

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1274

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1279

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Table 1: Summary of field intervention studies examining the prevalence and level of colonization (cecum/crop) of broiler flocks at slaughter age

Intervention	Stage of production used	Challenge: single or multiple strains, or natural	Observed effect on <i>Campylobacter</i> colonization					Commercial-scale trial or use		Effect on production parameters at any scale
			Prevent	Delay	Reduced at slaughter age and/or on carcasses	Other	Consistent effect?	Evidence of practical/logistic feasibility	Efficacious when trialed	
Shorter feed withdrawal / transport	<i>Terminal</i> : A	<i>Natural</i> : A	N/A	N/A	Yes: A		NK: A	Yes: A	NK	NK
Transport crate: raised mesh floor	<i>Terminal</i> : B	<i>Natural</i> : B	N/A	N/A	No: B		N/A	Yes: B	NK	NK
Acid-based antibacterial drinking water treatment	<i>Continuous</i> : C1, C2, C3, C4 ^a , C5 <i>Targeted</i> : C6 <i>Terminal</i> : C7	<i>Natural</i> : C3, C4 ^a , C5, C6 <i>Single</i> : C1, C2	Yes: C1 (indirect exposure ^b) No: C2, C3, C4 ^a , C7	No: C4 ^a	Yes: C3, C4 ^a , C5 No: C1, C2, C6, C7		No: C3, C5 NK: C4 ^a	Yes: C1, C2, C3, C4 ^a , C5, C6, C7	Yes: C3, C5 NK: C1, C6	NK: C1, C5, C6 Neutral: C2, C3, C7 Negative: C4 ^a (dose effect)
Non-acid-based antibacterial drinking water treatment	<i>Continuous</i> : C7, D1, D2	<i>Natural</i> : C7, D1, D2	No: C7, D1, D2	No: D2	Yes: D1 No: C7		Yes: D1	Yes: C7, D1, D2	Yes: D1 No: D2	NK: D1, D2 Neutral: C7
Acid-based antibacterial in feed	<i>Continuous</i> : C2, E1, E2, E3, E4	<i>Single</i> : C2, E1, E2, E3, E4	No: C2, E1, E2, E3	N/A	Yes: C2, E2, E3, E4 No: E1		Yes: E2 (small scale) No: C2, E3, E4	Yes: C2, E1, E3, E4	NK	Variable: E1, E3 Neutral: C2, E2
Non-acid-based feed treatment	<i>Continuous</i> : C2, C7, E3, F1, F2 <i>Targeted</i> : C2, C7 <i>Terminal</i> : F3	<i>Single</i> : C2, E3, F1 <i>Natural</i> : C7, F2, F3	No: C2, C7, E3, F1	Yes: F2	No: C2, C7, E3, F1, F2	Reduced numbers in crop: F3	Yes: F2, F3	Yes: C2, C7, E3, F2	NK: F2, F3	NK: F1 Neutral: C2, C7, E3 Improved: F2 N/A: F3
Diet structure / composition	<i>Continuous</i> : G1, G2	<i>Multiple</i> : G1 <i>Single</i> : G2	No: G1 NK: G2	Yes: G1 (via seeder birds), G2	Yes: G1		No: G1 (interaction with flooring type)	Yes: G1, G2	NK	Negative: G1
Bacteriocin, in water or feed	<i>Terminal</i> : H1 (mature), H2 <i>Targeted</i> : H1 (chicks)	<i>Natural</i> : H1 (mature), H2 <i>Single</i> : H1 (chicks)	See 'Other': H1 N/A: H2	N/A	Yes: H1, H2	Eliminated colonization: H1 (growing chicks)	NK: H1 (small number examined), H2	In-feed for 4-7 days: H1, H2 In water for 1-3 days: H1	NK	NK: H1 (chicks) N/A: H1, H2 (terminal use)

Table 1, continued: Summary of field intervention studies examining the prevalence and level of colonization (cecum/crop) of broiler flocks at slaughter age

Intervention	Stage of production used	Challenge: single or multiple strains, or natural	Observed effect on <i>Campylobacter</i> colonization					Commercial-scale trial or use		Effect on production parameters at any scale
			Prevent	Delay	Reduced at slaughter age and/or on carcasses	Other	Consistent effect?	Evidence of practical/logistic feasibility	Efficacious when trialed	
Bacteriophages dosed or in drinking water	<i>Targeted</i> : J1, J2, J3, J4, J5 <i>Terminal</i> : J6	<i>Single</i> : J1, J2, J3, J4, J5 <i>Natural</i> : J6	<i>No</i> : J1, J2, J3 <i>N/A</i> : J4, J5, J6	<i>Yes</i> : J1 (when given at time of challenge)	<i>Yes</i> : J1, J3, J6	Fewer shed (J2) or in caeca (J3, J4, J5)	<i>NK</i> : J2 (small numbers) <i>No</i> : J3, J4, J5, J6 <i>Yes</i> : J1	<i>Yes</i> : J6	<i>Yes</i> : J6	<i>NK</i> : J1, J2, J3, J4, J5, <i>N/A</i> : J6
Probiotic	<i>Continuous</i> : C7, E3, K1, K2, K4, K5 <i>Targeted</i> : K3 (from mid-rear) <i>Terminal</i> : K1	<i>Natural</i> : C7, K1, K2, K3, K5 <i>Single</i> : E3, K4	<i>No</i> : C7, E3, K1, K2, K3, K4, K5	<i>Yes</i> : K4 (only among young birds) <i>NK</i> : K5	<i>Yes</i> : E3, K1, K3, K4, K5 <i>No</i> : C7		<i>Yes</i> : K3 <i>No</i> : K2, K4 <i>NK</i> : K1, K5	<i>Yes</i> : C7, E3, K1, K2, K3, K4, K5	<i>Yes</i> : K2, K3, K4, K5	<i>Neutral</i> : C7, E3, K1, K2, K4 <i>NK</i> : K3, K5
Prebiotic	<i>Continuous</i> : C7, L1, L2, L3	<i>Natural</i> : C7, L2, L3 <i>Single</i> : L1	<i>No</i> : C7, L1, L2, L3	<i>Yes</i> : L1	<i>Yes</i> : L2 <i>No</i> : C7, L1, L3		<i>NK</i> : L1, L2 (limited detail)	<i>Yes</i> : C7, L2 <i>NK</i> : L1	<i>N/K</i>	<i>NK</i> : L2 <i>Neutral</i> : C7, L1, L3
Combination treatments ^c	<i>Continuous</i> : M1, M2 <i>Terminal</i> : C7	<i>Single</i> : M1, M2 <i>Natural</i> : C7	<i>No</i> : M1, M2	<i>No</i> : M1, M2	<i>Yes</i> : C7, M1 <i>No</i> : M2		<i>NK</i> : M1	<i>Yes</i> : C7, M1, M2	<i>N/K</i>	<i>NK</i> : M1, M2 <i>Neutral</i> : C7
Vaccination	<i>Targeted</i> : N1, N2, N3, N4, N5, N6, N7	<i>Single</i> : N1, N2, N3, N4, N5, N6, N7	<i>Yes</i> : N7 (parenteral) <i>No</i> : N1, N2, N3, N4, N5, N6, N7 (oral)	<i>No</i> : N1, N2, N3, N4, N5, N6, N7 (oral) (parenteral)	<i>Yes</i> : N1, N4, N5, N6 ^d , N7 (parenteral) <i>No</i> : N2, N3, N7 (oral)		<i>Yes</i> : N5 (transient) <i>NK</i> (small numbers): N1, N4, N7, N6	<i>Yes</i> : N3, N4, N6 (live attenuated <i>Salmonella</i> / <i>E. coli</i> vectors) <i>NK</i> : N1, N2, N3, N5, N7	<i>N/K</i>	<i>NK</i> : N1, N2, N3, N4, N5, N6, N7
Litter treatment	<i>Targeted</i> : P1, P2	<i>Natural</i> : P1, P2	<i>No</i> : P1, P2	<i>Yes</i> : P2	<i>No</i> : P1		<i>Yes</i> : P2	<i>Yes</i> : P1, P2	<i>Yes</i> : P2 <i>No</i> : P1	<i>NK</i> : P1, P2

NK: Not Known / Not Tested. *N/A*: Not applicable. ^a Caprylic acid derivative given in water PLUS feed. ^b Protection when colonized birds in adjacent pen, but not when seeder birds in same pen. ^c M1 & M2: Synbiotics (probiotic plus prebiotic), C7: organic acid water treatment plus clay feed additive. ^d Effect at 49 days but not at 42 days.

A: Northcutt et al., 2003. B: Buhr et al., 2000. C1: van Bunnik et al., 2012. C2: Gracia et al., 2016. C3: Jansen et al., 2014. C4: Hilmarsson et al., 2006. C5: Byrd et al., 2001. C6: Haughton et al., 2013. C7: Guyard-Nicodème et al., 2017. D1: Bügener et al., 2014. D2: Stern et al., 2002. E1: Hovorková & Skřivanová, 2015. E2: Molatová et al., 2011. E3: Guyard-Nicodème et al., 2016. E4: Thibodeau et al., 2014. F1: Johansen et al., 2006. F2: Kelly et al., 2017. F3: Epps et al., 2015. G1: Skånseng et al., 2013. G2: Nishii et al., 2015. H1: Svetoch et al., 2008. H2: Line et al., 2008. J1: Wagenaar et al., 2005. J2: Carvalho et al., 2010. J3: Loc Carrillo et al., 2005. J4: El-Shibiny et al., 2009. J5: Hammerl et al., 2014. J6: Kittler et al., 2013. K1: Cean et al., 2015. K2: Fritts et al., 2000. K3: Maruta et al., 1996. K4: Aho et al., 1992. K5: Smialek et al., 2018. L1: Molnár et al., 2015. L2: Y. Han, 2009. L3: Baurhoo et al., 2009. M1: Millán et al., 2015. M2: Baffoni et al., 2017. N1: Hodgins et al., 2015. N2: Kobierecka et al., 2016. N3: Łaniewski et al., 2013. N4: Nothaft et al., 2016. N5: Chintoan-Uta et al., 2016. N6: Buckley et al., 2010. N7: Annamalai et al., 2013. P1: Pope & Cherry, 2000. P2: Line & Bailey, 2006.