Gut Microbiota-targeted Interventions for Reducing the Incidence, Duration, and Severity of Respiratory Tract Infections in Healthy Non-elderly Adults

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ABSTRACT

Introduction:

Respiratory tract infections (RTI), such as those caused by influenza viruses and, more recently, the severe acute respiratory syndrome coronavirus-2, pose a significant burden to military health care systems and force readiness. The gut microbiota influences immune function, is malleable, and may provide a target for interventions aiming to reduce RTI burden. This narrative review summarizes existing evidence regarding the effectiveness of probiotics, prebiotics, and synbiotics, all of which are gut microbiota-targeted interventions, for reducing the burden of RTI in military-relevant populations (i.e., healthy non-elderly adults).

Materials and Methods:

A systematic search strategy was used to identify recent meta-analyses and systematic reviews of randomized controlled trials conducted in healthy non-elderly adults which examined effects of probiotics, prebiotics, or synbiotics on the incidence, duration, and/or severity of RTI, or on immune responses to vaccinations against viruses that cause RTI. Relevant randomized controlled clinical trials not included in those reports were also identified.

Results:

Meta-analyses and multiple randomized controlled trials have demonstrated that certain probiotic strains may reduce the incidence, duration, and/or severity of RTI and improve immune responses to vaccination against RTI-causing pathogens in various populations including healthy non-elderly adults. Fewer randomized controlled trials have examined the effects of prebiotics or synbiotics on RTI-related outcomes in healthy non-elderly adults. Nevertheless, some studies conducted within that population and other populations have observed that certain prebiotics and synbiotics reduce the incidence, duration, and/or severity of RTI or improve immune responses to vaccinations against RTI-causing viruses. However, across all product classes, not all product formulations have shown benefit, and most have not been tested in multiple randomized controlled trials in military-relevant populations.

Conclusion:

Dietary supplementation with certain gut microbiota-targeted interventions, and certain probiotics in particular, may provide viable strategies for reducing RTI-related illness in military personnel. Research in military populations is warranted to fully understand the magnitude of any military health and cost benefits, and to establish definitive recommendations for use.

INTRODUCTION

Globally, respiratory tract infections (RTI) and related diseases are leading causes of outpatient illness and are responsible for >2 million deaths annually.[1] Within the United States, RTI cause significant illness and mortality, being responsible for ~85,000 deaths per year.[2] That burden is also experienced within the U.S. military where infectious respiratory diseases account for up to 30% of infection-related military hospitalizations and have been estimated to impact up to 80,000 recruits and 600,000 active duty military personnel annually, resulting in 27,000 lost training days and 95,000 lost duty days per year.[3] This impact of RTI on military strength and readiness is not new. During World War I, more U.S. troops died from RTI and its complications than from battle injuries,[3] and, as recently as 2009, the novel A(H1N1)pgm09 virus was responsible for 20 to 30 hospitalizations weekly within the Military Health System.[4] Even more recently, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) has emerged as a highly contagious and virulent virus causing RTI with a high fatality rate.[5] The severity of disease that SARS-CoV2 causes, known as coronavirus disease (COVID)-19, has a tremendous public health burden and, along with other viruses causing RTI, carries the potential to reduce military

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strength, readiness, and lethality. As vaccine development is a lengthy process, and effectiveness of any vaccine will be variable,[6] it is imperative to identify immediate strategies that may mitigate risk of developing COVID-19 and other RTI, and which may reduce the duration and severity of illness following infection. Some have speculated that interventions targeting the gut microbiota may be one strategy.[7]

The human gastrointestinal tract is inhabited by trillions of microorganisms collectively known as the gut microbiota. These microbes largely coexist in a mutually beneficial relationship with their human host, carrying out functions the human body cannot and producing myriad compounds that modulate health and physiology.[8] For example, the gut microbiota is integral to deterring colonization of the gastrointestinal tract by pathogenic microbes.[9] Additionally, the location of the microbiota within the gastrointestinal tract places the community in close proximity to the largest collection of immune cells in the body, the gut-associated lymphoid tissue (GALT). A primary function of the GALT is to monitor and manage the gut microbiota and other antigens. As a result, the gut microbiota and human immune system constantly interact, with the immune system influencing the gut microbiota, and the gut microbiota influencing immune function.[10]

One implication of the dynamic bidirectional relationship between gut microbes and the immune system is that changes in the composition and metabolic activity of the gut microbiota can alter immune function, potentially altering host susceptibility to infection.[11] The modulation of susceptibility is not limited to gastrointestinal pathogens because the GALT interconnects with multiple arms of the innate and adaptive immune systems which are responsible for immune responses throughout the body, including within the pulmonary system.[10] Composition and metabolic activity of the gut microbiota is influenced by many factors. For example, military-relevant stressors may alter the gut microbiota in ways that could be beneficial to health and immune function in some cases, but detrimental in others.[12] Notably, initial military training and military deployment are sources of physical and psychological stress, and associated with high rates of RTI.[3] However, more so than stress, diet is a predominant mediator of gut microbiota composition and metabolic activity.[13] As a result, dietary interventions that target and modulate the gut microbiota may provide strategies for enhancing immune function before, during, and after stress.

Historically, the most common approaches for targeting and modulating the gut microbiota have included introducing new bacteria into the community and providing substrate to feed beneficial community members.[14] The former approach relies on probiotics, defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"[15] (Table I). In contrast, the latter approach relies on prebiotics, defined as "substrates (e.g., nutrients) that are selectively utilized by host microorganisms (e.g., gut microbes) conferring a health benefit."[16] Although there are few established prebiotics at present, several oligosaccharides, polysaccharides, and other compounds are considered "candidate prebiotics"[16] because their utilization by gut microbes is thought to result in a health benefit. Synbiotics are combinations of probiotics and prebiotics. Probiotics, prebiotics, and synbiotics modulate multiple aspects of local and systemic immune function in a variety of experimental models.[17,18] However, those effects and their mechanisms of action are not shared across all products (i.e., bacterial strains, or prebiotic type) or observed in every population studied, and effects on *in vitro, ex vivo*, or other measures of immune function do not necessarily translate to effects on infection and illness *in vivo*. As such, evidence synthesis and recommendations for use require attention to the form of the intervention itself, desired outcomes, and target population.

This report narratively summarizes evidence from systematic reviews, meta-analyses, and randomized controlled trials which have included military-relevant populations (i.e., healthy adults ~18 to 65 years), and have examined the effects of probiotics, prebiotics, and synbiotics on the incidence, duration, and severity of RTI, or on immune responses to vaccinations against viruses that cause RTI. The focus on healthy non-elderly adults is justified in that immune function and susceptibility to RTI is known to vary with age and health status.[19] The focus on immune responses to vaccination is justified by the substantial interindividual variability in immune responses to vaccination which impacts vaccine effectiveness,[20] evidence that the gut microbiota and gut microbiota-targeted interventions may influence that variability,[19] and the recognition that vaccine challenge models are a gold-standard method for measuring immune function.[21] Further, once a SARS-CoV2 vaccine is available, its use in military populations will be widespread and maximizing its effectiveness will be critical. Although it is unlikely that a single dietary intervention will prevent or eliminate COVID-19 or other viral diseases entirely, such interventions may provide safe, low-cost (relative to pharmaceuticals), and easily accessible strategies for reducing risk of infection and illness severity. Therefore, the aim of this review is to evaluate evidence regarding the use of probiotics, prebiotics, and synbiotics (i.e., gut microbiota-targeted interventions) for reducing RTI-related illness in military personnel.

METHODS

Relevant systematic reviews and meta-analyses published up to May 2020 were identified by searching PubMed using the search terms listed in Table S1. A similar search strategy was used to identify recently published randomized controlled trials not included in the systematic reviews. Reports that focused primarily or exclusively on infants, children <18 years, older-adult populations (>65 years), populations with an underlying chronic illness, or populations with an acute illness at the time the study started were not considered.

TABLE I. Probiotic Species and Prebiotic Compounds Studied for Reducing the Incidence, Duration, and Severity of Respiratory Tract Infections (RTI), or Enhancing the Immune Response to Vaccinations Against RTI-causing Pathogens in Healthy Non-elderly Adults

Product class	Probiotic species and prebiotic types studied	Potential impacts on gut microbiota	Potential effects on immune function[a]
Probiotics[b]	*Bifidobacteria:* *animalis* ssp. *lactis, bifidum, longum* ssp. *infantis* *Lactobacilli:* *acidophilus, brevis, casei, delbreueckii* ssp. *bulgaricus, fermentum, gasseri, helveticus, lactis, paracasei, plantarum, rhamnosus, salivarius* *Enterococcus faecium* *Streptococcus thermophilus*	Thought to be transient with minimal impact on overall diversity in healthy populations.[70] May help normalize microbiota after perturbation.[15]	↑Adaptive immune response; ↑Innate immune response; ↑Mucosal immunity; ↓Inflammation; ↑Gut barrier health; ↑Colonization resistance; ↑Cell-surface receptor (e.g., TLR) activation; ↑Organic acids
Prebiotics[c]	Fructans (inulin, fructo-oligosaccharides, oligofructose); Galactans (galacto-oligosaccharides)	↑Beneficial microbes and metabolites[16]	↑Adaptive immune response; ↑Mucosal immunity; ↓Inflammation; ↑Gut barrier health; ↑Colonization resistance; ↑Cell-surface receptor (e.g., TLR) activation ↑SCFA production

↓; decrease; ↑, increase; SCFA, short-chain fatty acid; TLR, Toll-like receptor.

[a]Potential effects are not necessarily shared across different probiotic strains or prebiotic types, nor have effects been consistently documented in human studies.[14,15,17,18,53]

[b]Examples of species limited to those investigated in randomized controlled trials of healthy non-elderly adults.

[c]Established prebiotics which, by definition, have been shown to selectively stimulate the growth and/or activity of a limited range of beneficial microbes.[16] Multiple other fermentable oligosaccharides and polysaccharides are known to stimulate the growth and/or activity of a broader population of microbes.

RESULTS AND DISCUSSION

Probiotics

Respiratory Tract Infections

Probiotics have a long history of safe use for a variety of clinical applications.[14,15] In a 2010 review focused on several military relevant health applications of probiotics including RTI prevention, Smith et al.[22] concluded that probiotics may reduce the duration and severity, but not the incidence, of RTI. However, the evidence at that time was not sufficiently robust for those authors to recommend procurement of any particular probiotic product(s) for distribution within military dining facilities. Since then, additional relevant studies on probiotic supplementation and RTI-related outcomes have been published (Tables II and S2). Evidence from some of those studies and others conducted up to 2014, which included ~4,000 participants, have been collated in 2 separate meta-analyses (Table II).[23,24] Those meta-analyses reported that probiotics reduced the number of individuals experiencing a RTI episode by 47%[23] and reduced the mean duration of RTI episodes by approximately 1 to 2 days.[23,24] However, both meta-analyses relied heavily on studies conducted in children, and both excluded studies conducted in athletes (a population relevant to military personnel). Comprehensive narrative and systematic reviews focused exclusively on probiotic use in athletes have concluded that ~65% of studies show favorable effects of probiotics on some aspect of immune function in athletes to include reducing the incidence, duration, and/or severity of RTI.[25–27] In one of those reviews, a position stand on probiotic use in athletes, the authors concluded that "specific probiotic strains can reduce the number of episodes, severity and duration of upper RTI" in athletic populations.[26]

For the purposes of the present report, we consolidated relevant studies captured in the meta-analyses and systematic reviews cited earlier with relevant recently published trials (Table S2). Of the 26 studies included, 38% (10 of 26), 45% (10 of 22), and 37% (7 of 19) reported that probiotics reduced the incidence, duration, or severity of RTI, respectively. While only 2 studies demonstrated favorable effects across all three outcomes (one of which reported favorable effects in men but detrimental effects in women), 62% (16 of 26) reported a favorable effect of probiotics on at least one of those outcomes. Single-strain relative to multi-strain supplements slightly more often reported at least one favorable effect (65% vs. 56% of trials), and interventions using single-strains of *Lactobacillus* more often reported at least one favorable effect (9 of 13 trials) when compared to interventions using single strains of *Bifidobacterium* (2 of 4 trials). Relatively few probiotic strains or multi-strain combinations were investigated in more than one study, and results were not always consistent in studies that did use the same strain/strain-combinations. These differential findings may be partly attributable to strain-specific effects and to other aspects of the study designs such as the duration and dose of supplementation, the populations studied, and uncontrolled lifestyle factors such as diet, sleep, smoking habits, and stress level. For example, *Lactobacillus*

TABLE II. Recent Meta-analyses Including Randomized Controlled Trials of Healthy Adults to Assess the Effects of Probiotics, Prebiotics, and/or Synbiotics on the Incidence, Duration, and/or Severity of Respiratory Tract Infections (RTI), or Immune Responses to Vaccinations Against RTI-causing Viruses

Reference	Studies included	Results
Probiotics		
King et al. 2014[24]	20 RCTs (8 in healthy non-elderly adults; excluded athletes) Population: Children and adults Intervention: *Bifidobacterium* or *Lactobacillus* probiotic Outcome: RTI incidence and duration	Probiotics reduced duration of illness episodes by 0.8 d [95% CI: 0.04 d, 1.5 d]; (9 studies, $n = 3,350$) Probiotics reduced days of illness by 0.3 d/person [95% CI: 0.1 d, 0.4 d]; (10 studies, $n = 2,647$) Probiotics reduced work/school days missed by 0.2 d [95% CI: 0.03 d, 0.3 d]; (10 studies, $n = 2,647$)
Hao et al. 2015[23]	13 RCTs (3 in healthy non-elderly adults; excluded athletes) Population: Children and adults Intervention: Any probiotic Outcome: RTI incidence and duration	Probiotics reduced odds of experiencing $\geq$1 RTI episodes by 47% [95% CI: 24%, 63%]; (7 studies, $n = 1,927$) Probiotics did not reduce the rate of RTI episodes (rate ratio = 0.83 [95% CI: 0.7, 1.05]; (5 studies, $n = 1,608$) Probiotics reduced duration of RTI episodes by 1.9 d [95% CI: 1.7 d, 2.0 d]; (3 studies, $n = 831$)
Lei et al. 2017[34], Yeh et al. 2018[35]	13 RCTs (5 in healthy non-elderly adults) Population: Healthy and hospitalized adults Intervention: Any probiotic Outcome: Immune responses to influenza vaccination	Probiotics increased odds of achieving seroprotection[a] against H3N2 (OR = 2.7 [95% CI: 1.2, 5.7]), but not H1N1 (OR = 1.7 [95% CI: 0.8, 3.8]) or B-strain (OR = 1.2 [95% CI: 0.6, 2.3]); (3 studies, $n = 155$) Probiotics increased odds of achieving seroconversion[b] against H3N2 (OR = 3.5 [95% CI: 1.4, 8.5]) and B-strain (OR = 2.2 [95% CI: 1.2, 4.1]) but not H1N1 (OR = 1.9 [95% CI: 0.7, 5.4]); (4 studies, $n = 362$) Probiotics increased antibody titers following H1N1 (mean difference from placebo = 4.7 [95% CI: 0.5, 8.9] and H3N2 (16.9 [95% CI: 0.9, 32.8]), but not B-strain (3.0 [95% − 0.8, 6.8]) vaccination; (7 studies, $n = 476$)
Prebiotics		
Lei et al. 2017[34], Yeh et al. 2018[35]	6 RCTs (1 in healthy non-elderly adults) Population: Healthy and hospitalized adults Intervention: Any prebiotic Outcome: Immune responses to influenza vaccination	Prebiotics increased odds of achieving seroprotection[a] against H3N2 (OR = 3.1 [95% CI: 1.2, 7.7]) and H1N1 (OR = 1.9 [95% CI: 1.1, 3.3]), but not B-strain (OR = 0.8 [95% CI: 0.5, 1.5]); (3 studies, $n = 215$) Prebiotics did not increase odds of achieving seroconversion[b] against H3N2 (OR = 1.3 [95% CI: 0.2, 8.0]), H1N1 (OR = 1.0 [95% CI: 0.5, 1.8]) or B-strain (OR = 1.8 [95% CI: 0.9, 2.6]); (2 studies, $n = 191$) Prebiotics increased antibody titers following H1N1 (mean difference from placebo = 35.5 [95% CI: 0.3, 70.0], but not H3N2 (18.7 [95% CI: −13.2, 50.6]) or B-strain (20.7 [95% CI: −9.1, 50.4]) vaccination; (5 studies, $n = 213$)
Synbiotics		
Chan et al. 2020[58]	16 RCTs (2 in healthy non-elderly adults) Population: Healthy, any age Intervention: Any synbiotic Outcome: RTI incidence	Synbiotics reduced the rate of RTI by 16% [95% CI: 4%, 27%]; (9 studies, $n = 2,845$) Synbiotics reduced the risk of RTI by 16% [95% CI: 5%, 26%]; (7 studies, $n = 7,273$)

CI, confidence interval; d, days; OR, odds ratio; RCT, randomized controlled trial; RTI, respiratory tract infection.

[a]Seroprotection is defined as an antibody titer superior to an established threshold for clinical protection against the virus.[21]

[b]Seroconversion is defined as achieving a certain fold increase (e.g., 4-fold) in specific antibody titers after vaccination.[21]

fermentum VRI-003 (PCC) reduced RTI duration and severity in men in two separate studies but increased RTI incidence, duration, and severity in women in one of the studies.[28,29] The one strain for which favorable effects were observed in multiple studies was *Lactobacillus casei* Shirota. That strain, when administered in a fermented milk product, reduced the incidence of RTI in three of four studies.[30–33] In the single study in which RTI incidence was not reduced, the overall incidence was unexpectedly low and antibody titers to cytomegalovirus and Epstein–Barr virus were reduced by *L. casei* Shirota suggesting an immune benefit from the probiotic intervention.[31]

Vaccine Responses

The response to vaccination is mediated by innate, humoral, and cell-mediated immunity, and can be assessed using a variety of measures including antibody titers, seroconversion rates, seroprotection rates, and/or vaccine-specific immunoglobulin concentrations (see Table II legend for definition of seroconversion and seroprotection).[19] Several studies have examined whether probiotics improve immune responses to vaccinations against viruses that cause RTI, most often examining vaccine responses against seasonal influenza strains (H1N1, H3N2, and B-strain) (Table S3). Results from many of those studies have been collated in two recent meta-analyses[34,35] and a systematic review.[36] In one meta-analysis,[34] probiotics were found to increase the odds of achieving seroprotection following H3N2, but not H1N1 or B-strain vaccination, and increase the odds of seroconversion following H3N2 and B-strain, but not H1N1 vaccination (Table II). A separate meta-analysis reported that probiotics increased antibody titers following H1N1 and H3N2, but not B-strain, vaccination (Table II).[35] However, both meta-analyses included elderly and hospitalized patients, and excluded the largest relevant trial. That trial of 1,099 healthy young and middle-age adults found no effect of *Lactobacillus paracasei* ssp. *paracasei* 431 (L. casei 431) supplementation on any measure of vaccine responsiveness or the incidence of postvaccination RTI.[37] However, the duration of postvaccination RTIs were reduced by ∼1 day,[37] and the same probiotic strain improved antibody responses to vaccination in a smaller trial.[38] Further, all other studies conducted in healthy non-elderly adult populations have reported favorable effects of probiotics on at least one outcome related to immune responses to influenza vaccinations, though favorable effects are rarely seen against all influenza strains tested (Table S3). Two additional studies of healthy young and middle-age adults have also reported that various probiotics increased concentrations of vaccine-specific antibody responses following vaccination against polio[39] and hepatitis A[40] viruses. Collectively, these observations are consistent with recent reviews examining the entire evidence base (neonates through elderly adults and all types of vaccines) which have concluded that probiotic interventions can likely improve vaccine efficacy and that future research should focus on defining optimal strains/strain-combinations and dosing regimens.[36,41]

Probiotics Summary

The evidence reviewed above collectively demonstrates that probiotics show promise for reducing the incidence, duration, and/or severity of RTI and improving immune responses to vaccinations against RTI-causing viruses in healthy non-elderly adults. However, benefits have not been observed with all strain/strain-combinations tested which is consistent with the concept that immunomodulatory effects of probiotics are likely strain-specific.[15] Results from vaccination trials similarly suggest that not all probiotics are effective against all viral strains. Therefore, not all probiotics available in the marketplace should be expected to protect against RTI or improve vaccine responsiveness. That conclusion is consistent with the findings of recent meta-analyses suggesting that probiotics overall appear to modestly reduce RTI incidence, duration, and/or severity in infants and children, but that evidence is stronger for certain strains, such as *Lactobacillus rhamnosus* GG, than others.[42–44]

Meta-analyses focused on studies conducted solely in healthy non-elderly adults are notably absent from the evidence base. Therefore, despite promise, the magnitude of benefit for military populations is uncertain and the most effective strains/strain combinations and dosing regimens are unclear. Nonetheless, the modest benefits reported in meta-analyses of studies conducted to date do have the potential to substantially reduce military health care burden and costs. In support, a recent mathematical modelling analysis based on 2 of the meta-analyses reviewed herein[23,24] estimated that if the entire U.S. population were to take probiotics, the total number of sick days due to RTI would be reduced 10% to 25% annually at an estimated cost savings of up to $1.4 billion when productivity loss is included.[45] Effect estimates included a 50% to 60% reduction in RTI-related sick days in unvaccinated individuals (e.g., SARS-CoV2) and those sharing indoor environments (e.g., military barracks).[45] While confirming such an analysis is impossible, and limitations included assuming that all probiotic formulations are equally effective and not accounting for costs of the probiotics themselves, the analysis does make the point that probiotics may provide a cost-efficient option for reducing RTI burden, particularly in high-risk groups. Also worth noting in the context of the COVID-19 pandemic are results from recent meta-analyses which concluded that probiotics reduce the incidence of ventilator-associated pneumonia in patients on mechanical ventilation[46] and reduce the duration of diarrhea and hospitalization because of viral gastroenteritis.[47] Consumption of probiotics that have shown benefit for reducing RTI incidence, duration, and/or severity, or improving vaccine responses in at least one well-conducted human trial, such as *L. casei* Shirota, should therefore not be

discouraged in healthy adults if the product is obtained from a reputable source. Recent reviews provide excellent guidance on considerations for identifying reputable probiotic supplements.[48] However, large, well-designed studies[49] conducted in military populations at high risk for RTI are ultimately needed to enable more definitive recommendations regarding the most effective probiotic strain, strain combinations, and dosing regimens for improving RTI-related outcomes in military personnel.

Prebiotics

Current established prebiotics are listed in Table I. All are fermentable (by bacteria) carbohydrates selectively utilized by *Bifidobacterium* and/or *Lactobacillus*. These carbohydrates are naturally occurring in plants, extracted from plants and added to foods, or synthesized for food ingredient and dietary supplement use.[50] Other fermentable carbohydrates and phenolic compounds found in fruits, vegetables, and whole grains are metabolized by and modulate the gut microbiota, and the health promoting properties of some may be mediated, in part, by gut microbes.[16] However, for the purposes of this review, we focus primarily on established prebiotics.

Respiratory Tract Infections

Despite the role of prebiotics in stimulating bacterial genera commonly used in probiotic supplements, only one study was identified that has examined effects of established prebiotics on RTI in healthy non-elderly adults (Table S4). In that study, dose-response effects of galacto-oligosaccharides on RTI symptoms were not observed and effects varied by stress level and body weight status.[51] The paucity of studies examining effects of established prebiotics on RTI incidence, duration, and severity in healthy non-elderly adults is somewhat surprising as biological plausibility for immunomodulation has been demonstrated in animal studies, and favorable effects have been observed in some studies of infants, children and, to a lesser extent, elderly and critically-ill adults (reviewed in Refs. 17, 52, and 53). Of note, evidence suggests that certain nondigestible fermentable carbohydrates and plant-derived phenolic compounds that modulate the gut microbiota in a nonselective manner, or are metabolized and biotransformed by the gut microbiota, may have some efficacy for reducing RTI incidence, duration, and/or severity.[54,55] For example, a 2016 meta-analysis of 6 studies which included 531 volunteers found that plant phenolics known as flavonoids reduced the incidence of RTI in healthy non-elderly adults by 33%.[54] This evidence is consistent with the concept that immunomodulatory properties of prebiotics and related compounds are attributable to both metabolites produced from those compounds by gut microbes in addition to those compounds promoting the growth of beneficial microbes, and suggests that many combinations of dietary components could impact RTI-related outcomes through effects on the gut microbiota.

Vaccine Responses

Studies examining effects of established prebiotics on immune responses to vaccinations against RTI-causing viruses have been collated in two recent meta-analyses.[34,35] In the first, prebiotics were found to increase the odds of achieving H1N1 and H3N2, but not B-strain, seroprotection following vaccination, but had no effect on seroconversion rates (Table II).[34] The second meta-analysis reported that prebiotics increased postvaccination antibody titers for H1N1, but not H3N2 or B strains (Table II).[35] Only one study included in those meta-analyses was conducted in a healthy non-elderly adult population, and, in that study, no effects of long-chain inulin and oligofructose supplementation on the immune response to vaccination were observed (Table S3).[56] Similar to the evidence base related to RTI, certain nondigestible fermentable carbohydrates and plant-derived phenolic compounds that modulate or are metabolized by the gut microbiota have shown favorable effects on immune responses to vaccination, though many of the studies were not conducted in healthy non-elderly adult populations.[52,57] Thus, while some evidence suggests potential for prebiotics and related compounds to improve immune responses to vaccination, effects may be specific to the pathogenic agent, and whether these effects are present in healthy non-elderly adults is not well characterized.

Synbiotics

Synbiotics are, in theory, designed to provide complementary, additive, or synergistic effects of their probiotic and prebiotic constituents, and can include many different combinations of beneficial microbes and prebiotic ingredients. One recent systematic review and meta-analysis identified 16 studies including 10,443 participants which examined the effects of synbiotics on RTI incidence, duration, and/or severity.[58] Results demonstrated that synbiotic interventions reduced the incidence rate of RTI and the proportion of participants who experienced a RTI by 16% (Table II).[58] Only two reports included in the meta-analysis described studies conducted in adult populations. However, one of those reports described three separate large randomized controlled trials comparing similar synbiotic supplements to placebos, and all three of those trials showed reductions in the incidence, duration, and severity of RTI with synbiotic supplementation (Table S4).[59] Evidence that synbiotics impact vaccine responses against RTI-causing viruses in adults is similarly limited to a single trial which found no benefit.[60] As such, too few studies exist to draw any conclusions regarding the effect of synbiotic supplements on RTI-related outcomes in healthy non-elderly adults.

Prebiotics and Synbiotics Summary

Relative to probiotics, far fewer randomized controlled trials have determined the effects of established prebiotics or synbiotics on the incidence, duration, and/or severity of RTI,

or on immune responses to vaccinations against RTI-causing viruses in healthy non-elderly adults. However, recent systematic reviews and meta-analyses provide some evidence supporting the efficacy of prebiotic and/or synbiotic products for these purposes in infant, child, and/or elderly adult populations.[34,35,58] Additional evidence suggests that certain nondigestible fermentable carbohydrates and plant-derived phenolic compounds that modulate the gut microbiota in a nonselective manner, or are metabolized and biotransformed by the gut microbiota, may also have some efficacy for reducing RTI incidence, duration, and/or severity.[52,54,57] Thus, research in healthy non-elderly adult populations, to include military personnel, is warranted. Considering the large variety of nutrients known to modulate or be modulated by the gut microbiota, these studies need not focus solely on established prebiotics.

CONCLUSION

Infectious respiratory disease burden is high in military personnel, a population which is exposed to a variety of different stressors that compromise immune function possibly due, in part, to effects of those stressors on the gut microbiota.[12] Dietary supplements targeting the gut microbiota may, in theory, mitigate RTI-related illnesses by increasing proportions of beneficial microbes and beneficial microbiota-derived metabolites within the gut microbiota, which can be achieved through the introduction of exogenous microbes (probiotics), feeding beneficial microbes (prebiotics), or their combination (synbiotics). A growing and diverse evidence base has examined the efficacy of probiotics, and to a lesser extent prebiotics and synbiotics, for reducing the incidence, duration, and/or severity of RTI, and for improving immune responses to vaccinations against RTI-causing viruses. Although promising results exist for certain interventions and within certain populations, few studies have been conducted in military populations.[61,62] Trials conducted in military-relevant populations (i.e., healthy non-elderly adults) have studied multiple different product formulations, and, in some cases, reported different results using the same formulations. As a result, there is not sufficient evidence at this time to recommend the use of any particular product formulation(s) for RTI risk reduction in military personnel.

Currently, no singular diet or dietary intervention can prevent or cure RTI and associated sequelae caused by any virus including SARS-CoV2. However, reducing risk and illness severity would reduce health care burden, and, within the military, increase force readiness. Notably, the magnitude of reduction in RTI incidence and duration attributed to probiotics in different meta-analyses is similar to, if not better than, the effects achieved through dietary supplementation with vitamins C and D, zinc, and Echinacea which are commonly used remedies for RTI.[63–66] Further, although not reviewed herein, some gut microbiota-targeted interventions, primarily probiotics, have demonstrated potential for reducing the incidence, duration, and severity of gastrointestinal tract infections.[47,67,68] Like respiratory infections, gastrointestinal infections represent a significant burden on the military health care system and force readiness.[69] Thus, accumulating evidence from meta-analyses and randomized controlled trials support the conclusion that dietary supplementation with gut microbiota-targeted interventions, and certain probiotic strains in particular, can provide a promising safe and accessible strategy for reducing the burden that multiple infectious diseases pose for military health care and force readiness. Although reductions at the individual level appear to be modest, when extrapolated to the entire military population, reductions in health care burden and costs could be significant. To fully understand that promise, and the associated magnitude of any risk reduction and cost-benefits for military personnel, research in military populations, particularly those at high risk for RTI, is needed. Until then, the probiotics and prebiotics investigated in studies reviewed herein which have demonstrated beneficial effects in one or more studies (see Supplemental Tables) can be considered viable options for military personnel interested in reducing RTI-related illness.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

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CONFLICT OF INTEREST

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