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The Effects of Dairy Consumption on Vaccine Immune Response and Immunoglobulins: A Systematic Literature Review

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Abstract

Public health interest in vaccinations and immune protection has increased with the COVID-19 pandemic. Dairy products are an important source of protein and other nutrients, and there are unresolved research questions regarding the potential health impact of dairy products on the enhancement of immune response. A systematic literature review was conducted to synthesize the published literature reporting the effects of dairy interventions on: 1) the vaccine-specific immune response and 2) immunoglobulins in the absence of vaccination. To assess study validity and quality, we used the Academy of Nutrition and Dietetics Quality Criteria Checklist. Sixty-one studies (59 clinical trials, 1 cohort, 1 cross-sectional survey) were included, spanning 1983-2017. Ten trials evaluated the effect of dairy intervention on vaccine-specific IgG, IgA, IgM, vaccine-specific antibody titers, seroprotection rates, or seroconversion rates. Of these, 7 reported significant increases with dairy interventions for post-vaccine tetanus antibodies, mean change in tetanus antibody level, total antibody titers to flagellin from *Salmonella Adelaide,* mean antibody titers to influenza B, influenza-specific IgA and IgG levels, and seroconversion or seroprotection rates for influenza A and B. Fifty-six studies evaluated dairy's effects on immunoglobulins without vaccinations. The results were heterogenous, with some studies reporting significant enhancement of immunoglobulins (IgA, IgE, or IgG), while others observed no differences between groups. Clinical relevance of the immunoglobulin changes was not investigated in these studies. Dairy products and their components could enhance the efficacy of vaccines. This review highlights the evidence gaps and provides a potential roadmap for additional research.

Introduction

The potential benefits of dietary patterns and specific foods are of great interest to researchers, including nutritional intervention for overall health improvement, disease prevention, and symptom management [1-3]. In various dietary guidelines, dairy products are considered as an important source of protein and other nutrients including vitamin D and calcium [4,5]. The ability of dairy products and/or their

components to enhance immune response may be an important aspect of dairy's influences on health [6-8].

The potential immune-modulating effects of dairy products and their components have been considered in *in vivo* and *in vitro* models, including the role of probiotics [9-11]. The findings in these models suggest a beneficial role of probiotics on immunity through various proposed mechanisms, including a direct impact on pathogens by competing for colonization of the gut's epithelium and the stimulation of the innate immune response in the gut (e.g., modulating the release of cytokines to promote defense) [10]. Likewise, the whey protein lactoferrin may provide beneficial impacts with improved immunity, resistance to infection, and stimulation of the anti-inflammatory immune response [12]. With regard to epidemiologic research on dairy products/components, recent systematic reviews and meta-analyses have concluded that there may be a neutral to positive benefit of whole dairy products, probiotics and proteins on biomarkers of inflammation [8,13-15].

While there is a notable body of work regarding the impact of dairy products/components on immune functions, overall conclusions are not clear. As such, we conducted a systematic literature review to identify and synthesize existing literature on the effects of dairy products and their components on immune-related outcomes, excluding biomarkers of inflammation (PROSPERO: CRD42022333780). During our assessment of the available outcome data, vaccine response was identified as an outcome with available evidence. Given the increased focus on vaccinations with the onset of the COVID-19 pandemic, this systematic literature review examined the available evidence on the potential for whole dairy products/components to enhance the antibody response after vaccination. To complement this assessment, we also systematically evaluated the evidence for the effects of dairy products and their components on immunoglobulins in the absence of vaccination.

Methods

We followed the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines during the conduct and reporting of this review [16]. PRISMA checklist was submitted (Supplemental Material). Our protocol was registered prior to study conduct at the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022333780). The registered protocol described a comprehensive literature search strategy, with search terms for dairy exposures and outcomes relevant to non-inflammatory immune outcomes. This review was conducted to identify the available evidence and rank the sufficiency of the evidence on the available outcomes. Herein, we summarize the evidence related to nutritional interventions with dairy products/components and 1) the immune response to vaccination and 2) the immunoglobulin response in general. Following PRISMA procedures and as specified in the registered protocol, other outcomes related to non-inflammatory immune function will be presented in future publications.

Eligibility Criteria

The eligibility criteria were developed based on the population, interventions, comparator, outcomes, and study design (PICOS) elements.

Population

This review included epidemiologic studies of all populations, excluding studies investigating persons with dairy sensitivity. There were no restrictions on geographical location, sex, age, or health status.

Interventions

We included studies of exposure or dietary intervention involving whole dairy products, dairy proteins,

or other components of dairy. Whole dairy products of interest included cow's milk, yogurt, and cheese (both standard products and those fermented with additional probiotics). Yogurts using the traditional starter cultures *Lactobacillus (L.) bulgaricus* and *Streptococcus (S.) thermophilus* were referred to as traditional yogurt, while probiotic yogurts were those with additional probiotics added. Dairy proteins included whey (soluble milk protein) and casein (insoluble milk protein). Other dairy components of relevance were the fat components of milk (i.e., milk phospholipids and the milk fat globular membrane). Milk powders, milk peptides/proteins, and dairy products fermented with experimental/ non-traditional bacterial strains were considered relevant. Studies assessing dietary patterns, including prenatal and maternal exposures, were included. Studies where dairy products or components were administered through a feeding tube were included. Studies of bovine colostrum, non-bovine milks, hyperimmunized milk, and raw/unpasteurized milk were excluded. Studies that administered probiotics alone or in a vehicle other than a dairy product were also excluded. Studies that did not calculate an effect estimate or conduct any statistical comparisons were excluded.

Comparator

Studies were required to have comparison group(s) of low or no dairy product/component consumption or pre- and post-intervention outcomes.

Outcomes

The registered protocol for the systematic literature review specified all outcomes related to immune function, excluding biomarkers of inflammation (which have been reviewed previously [8,14]) and outcomes related to milk allergies/sensitivities. In this publication, we evaluated the following outcomes reported in the included studies: 1) immunoglobulin levels (IgA, IgD, IgE, IgG, and/or IgM) in the absence of vaccination; and/or 2) immunological responses to vaccines, specifically vaccine-specific immunoglobulins, vaccine-specific antibody titers, seroprotection rates, and/or seroconversion rates. Antibody titers are used to assess immunogenicity of various vaccines (e.g., the hemagglutinin inhibition [HI] titer for influenza) [17]. The seroprotection rate refers to the proportion of individuals reaching an established protective antibody titer level (e.g., 1:40 for influenza, which is associated with a 50% reduction in the risk of acquiring laboratory-confirmed influenza), while the seroconversion rate describes the proportion of patients that reach a predefined increase in the HI titer that indicates a response (e.g., fourfold for influenza) [18].

Study Design

The publication start date was not restricted. This review included peer-reviewed publications with the following study designs: prospective or retrospective cohort studies, case-control studies, cross-sectional studies, and clinical trials. Reviews, meta-analyses, case series, and case reports were excluded. Conference abstracts and articles for which neither the abstract nor the full text were available in English were excluded.

If more than one article from the same study population were published, data from the publication with the longest follow-up or most relevant population and/or outcomes were evaluated. For studies with overlapping data, data from the publication with the larger population size or most relevant population and/or outcomes were considered.

Study Identification and Screening

The pre-determined literature search strategy was followed at all stages of the review. Searches were

conducted in the PubMed and Embase databases on May 19, 2022, with the human and English language filters applied (Supplemental Table 1). Standard software to conduct systematic literature reviews, i.e., DistillerSR (Version 2023.4) [19], was used to deduplicate the literature search results from PubMed and Embase and to track the identified publications at each stage of review.

One reviewer examined the titles and abstracts of the deduplicated articles for inclusion based on the eligibility criteria. The articles considered to be relevant at the title and abstract level were independently evaluated at the full-text level by 2 reviewers; all conflicts were resolved by a senior reviewer. Following the PRISMA guidelines, bibliographies of relevant reviews were also assessed to identify any additional citations of interest meeting the PICOS elements.

Data Abstraction

In DistillerSR, data abstraction was conducted for all included studies. The following information was abstracted for each included study: study design; geographical location(s); study period; dairy product (s)/component(s) under evaluation; dosing and duration; population size; health status; age range; immunoglobulin levels measured (IgA, IgD, IgE, IgG, and/or IgM); and the vaccine administered and concurrent or subsequent effects on immunoglobulins, vaccine-specific antibody titers, seroprotection rates, and/or seroconversion rates. Any relevant effect estimates, confidence intervals, and statistical testing for these outcomes were abstracted.

One reviewer conducted data abstraction, while a second reviewer independently reviewed the entries for complete quality control. All conflicts were resolved by a senior reviewer.

Risk of Bias Assessments

Risk of bias (RoB) assessment was also conducted for all included studies. To assess study validity and quality, we used the Academy of Nutrition and Dietetics Quality Criteria Checklist [20]. This tool examined several domains pertaining to relevance, validity, and bias due to funding source. RoB assessment was conducted by one reviewer; the results were reviewed independently by a second reviewer (100% quality control). A senior reviewer resolved any conflicts and finalized the RoB results. Study quality was determined as positive, neutral, or negative, depending upon the scoring results from the domains (Supplemental Table 2).

Data Synthesis

For each outcome, we systematically summarized the data by study quality, dairy exposure/intervention, and publication year. Qualitative synthesis was done, as meta-analysis could not be performed due to the heterogeneous nature of the dairy exposures and reported outcomes.

Results

The PRISMA flow diagram describes the inclusion and exclusion of studies at each step of the review; 6145 and 6828 records were identified in PubMed and Embase, respectively (Figure 1). Using de-duplication in DistillerSR, 9382 records were screened at the title and abstract level. At the full-text level, 405 (389 references identified from title and abstract screening and 16 references identified from evaluations of relevant review articles) publications were reviewed, with 189 total references determined to be eligible. Among the 189 studies, 61 publications described the impact of dairy exposure/ components on the vaccine-specific immune response and immunoglobins without vaccinations; the remaining publications examined outcomes that will be reported in future publications.

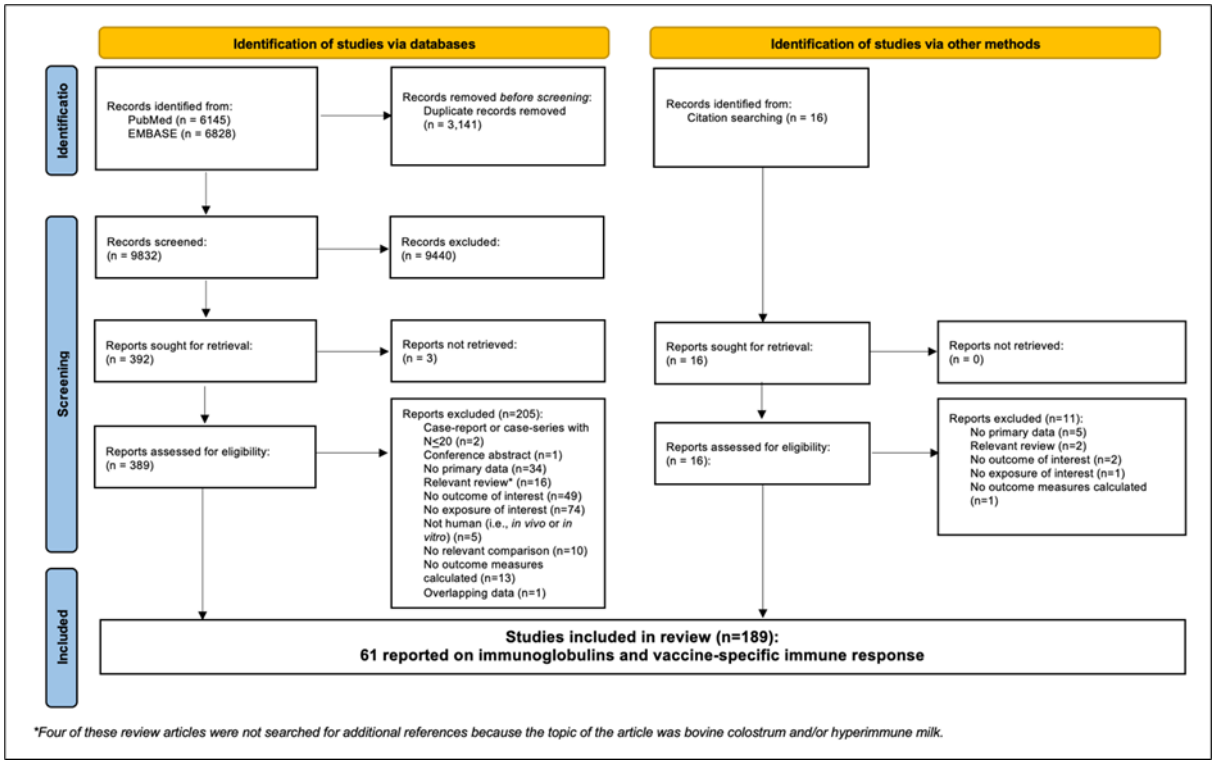

Figure 1. PRISMA Flow Diagram

*Four of the relevant review articles were not further searched for additional references as the exposures were not relevant (i.e., bovine colostrum and/or hyperimmune milk).

Source of flow diagram template: Page et al. 2021 (16).

Characteristics of Included Studies (N=61)

Table 1 presents the characteristics of the 61 studies: 27 (44.3%) were determined to have positive study quality, 33 (54.1%) were determined to have neutral quality, while one study (1.6%) [21] was determined to have negative quality. Except for one cross-sectional survey [22] and one cohort study [23], the remaining 59 studies were clinical trials. Four studies provided vaccine-specific immunological response data only [24-27], 50 studies reported the effects of dairy on immunoglobulin levels without vaccinations only, and 6 presented results on both outcome types [28-33]. The period of study enrollment and follow-up was not reported in 32 studies; of those providing enrollment and follow-up data (n=29), the years ranged from 1983 to 2017. Fifty-nine studies reported geographical location, with 80% (n=47) conducted in European nations.

Effect of Dairy Intervention on the Immune Response to Vaccination (N=10)

Ten clinical trials evaluated dairy interventions in conjunction with vaccination and their effect on vaccine-specific IgG, IgA, IgM, and antibody titers, seroprotection rates, and/or seroconversion rates [24-33] (Tables 1). Among 5 trials specifying the study enrollment and follow-up period, the years ranged from 2005 to 2011 [24,25,29-31] (Table 1). The vaccines studied included diphtheria [27,30,33], tetanus [27,30,33],

pertussis [27,30], polio [26,30,32], influenza [24,25,29,31], hepatitis B [33], *Haemophilus influenzae type B* [30,33], flagellin from *Salmonella adelaide* [28], and *Streptococcus pneumoniae* or *pneumococcus* [30,32], with studies often administering combination or multiple vaccines (Table 2). Four trials were conducted in hospitalized elderly patients [24,25,27,29], while 3 were in adults (healthy: N=2; allergy: N=1) [26,31,32] and 3 were in infants and children (healthy: N=2; stunted growth: N=1) [28,30,33] (Table 2).

In 3 trials, differences between treatment arms were not observed in any of the reported analyses [30,32,33] (Table 2). The remaining 7 trials reported differences between the treatment arms or between pre- and post-intervention periods for at least one outcome. These 7 studies are described in the upcoming sections by the dairy product/component intervention [24-29,31] (Table 2).

Overall, the evidence base indicated that whole dairy products enhanced vaccine-specific immune response to tetanus and *Salmonella Adelaide*, while probiotics added to whole dairy products amplified vaccine-specific immune response to influenza and polio.

Whole dairy products

Two trials evaluated changes in vaccine-specific antibody titers following milk powder consumption [27,28]; study years were not reported in either trial (Tables 1 and 2).

Elderly patients in retirement centers and long-term care facilities in the United States were given 6 g milk powder (n=10) or isoflavone soy protein (n=11) twice daily for 8 weeks and administered the diphtheria, tetanus, and pertussis (DTaP) vaccine at week 4 [27] (Table 2). Post-vaccine tetanus antibodies were higher in the milk powder intervention compared with the soy protein group at week 8 ($p=0.034$). The mean change in the tetanus antibody level was also higher in the milk powder group ($p=0.029$).

Prepubertal children in New Guinea with growth deficiencies were given skim milk powder (n=30) or no intervention (n=24) for 8 months and administered flagellin (i.e., protein) from *Salmonella adelaide* at month 7 [28] (Table 2). Total antibody titers at 6-weeks post-vaccination were higher in the skim milk powder group compared with the untreated group ($p=0.002$).

Whole dairy products with added probiotics

Five trials evaluated whether probiotics added to dairy products altered the immune response to vaccination, including 4 studies administering an influenza vaccine [24,25,29,31] and one administering the polio vaccine [26] (Table 2).

During the 2010-2011 season, enterally-fed elderly patients in Japan were given a milk-based formula with added prebiotics and probiotics (*L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus*) (n=12) or a standard milk-based formula (n=12) for 14 weeks, with H1N1/H3N2/B influenza vaccination at week 4 [29] (Table 2). The antibody titer to the influenza B antigen was lower in the intervention group compared to the control group at weeks 6 and 8 ($p<0.05$).

During the 2006/2007 influenza vaccine campaign in Spain, study participants aged 65-85 years received trivalent influenza vaccines [25] (Table 2). Probiotic consumption was started 3-4 months after vaccination. Nineteen elderly patients were randomized to high-dose skim milk powder with *L. plantarum* CECT 7315/7316, 14 were randomized to low-dose skim milk powder with *L. plantarum* CECT 7315/7316, and 15 were randomized to skim milk powder without the probiotic; the milk powders were administered for 3 months. For each treatment arm, the investigators compared immunoglobulin

levels in the post- vs. pre-intervention. An increase in influenza-specific IgG was observed only for the high-dose intervention arm, comparing the post- vs. pre-intervention levels (p=0.023). Influenza-specific IgA was increased in both the high- and low-dose intervention arms, comparing post- vs. pre-intervention levels (p=0.008 and p=0.039, respectively).

During the 2008-2009 influenza season, healthy adults in Italy were randomized to 4 intervention arms. Two treatment groups were relevant for this review with 56 receiving an acidified dairy drink containing *L. paracasei* ssp. *paracasei (L. casei* 431*)* and 54 receiving a placebo acidified dairy drink for 6 weeks [31] (Table 2). The trial participants were also administered the A/H1N1/A/H3N2/B influenza vaccine 2 weeks after starting the dairy intervention. Change between post-intervention and baseline plasma levels of influenza vaccine-specific total IgG, IgG1 and IgG3 were higher in the intervention group compared with the placebo (p=0.01, p<0.01, and p<0.001, respectively). The plasma IgG1 and IgG3 seroconversion rates were higher in the intervention group, compared to the placebo (p<0.001 and p<0.001, respectively).

A trial was conducted in France during the 2005-2006 (pilot study) and 2006-2007 (confirmatory study) influenza seasons [24] (Table 2). Differences between groups were observed in the confirmatory study only. In the confirmatory study, 113 participants were given a traditionally fermented dairy drink containing *L. casei* DN-114 001 (along with the traditional ferments of *S. thermophilus* and *L. bulgaricus*) for 13 weeks, and 109 were given non-fermented dairy drink. The influenza vaccine (A/H1N1, A/H3N2, and B) was administered 4 weeks after starting the consumption of the study products. The geometric mean antibody titers for the B strain were higher at 3 weeks (p=0.029), 6 weeks (p=0.027), and 9 weeks (p=0.025) after vaccination in the intervention arm, compared with the placebo. The seroconversion rate at 5 months after vaccination was also higher in the intervention arm, compared with the placebo for the B and A/H3N2 strains only (p=0.016 and p=0.031, respectively). The seroprotection rate at 3 weeks after vaccination in a subgroup of participants who were non-seroprotected at baseline was increased in the intervention group, compared to the placebo, for the A/H1N1 strain only (p=0.045).

In Germany, 22 healthy adults were given 100 g acidified milk product containing *L. rhamnosus* GG (LGG) (intervention 1) daily, 21 were given the same milk product with *L. acidophilus paracasei* subspecies *paracasei* (CRL431) (intervention 2) daily, and 20 received placebo acidified milk product [26] (Table 2). The treatment period spanned over 5 weeks for both intervention arms; the study year was not reported. Oral polio vaccination occurred at day 8. The poliovirus-1 IgA titer was increased in intervention arm 1 (p=0.036) and the poliovirus-2 IgM titer was increased in intervention arm 2 (p=0.040), compared to the placebo. Increased neutralizing antibodies of poliovirus-1 and -2 were also found with intervention arm 1, compared with the placebo (p=0.048 and p =0.014, respectively). Increased neutralizing antibodies were observed for poliovirus-3 (p=0.011), with intervention arm 2 compared to the placebo.

Effects of Dairy Intervention on Immunoglobulins (N=55)

Fifty-six studies evaluated dairy's effects on immunoglobulins without vaccinations. The results were heterogenous, with some studies reporting significant enhancement of immunoglobulins (IgA, IgE, or IgG), while others observed no differences between treatment groups. Supplemental Table 3 presents the immunoglobulin information reported in these 56 studies. Supplemental Materials provide detailed summaries of the evidence.

Table 1. Characteristics of Included Studies, Organized by Study Quality, Dairy Exposure, and Publication Year (N=61)

Author (Year)	Study Design	Geographical Location	Study Period	Dairy Product or Component	Study Outcome	Study Quality
Suzuki (2020) [37]	Clinical trial	Japan	NR	Whole dairy: probiotic yogurt	IgE	Positive
Schaefer (2018) [27]	Clinical trial	United States	NR	Whole dairy: milk powder	Vaccine-specific response: Antibody titers to vaccines	Positive
Pu (2017) [38]	Clinical trial	China	Both enrollment and follow-up: 2013	Whole dairy: probiotic yogurt	IgA, IgE, IgG, IgM	Positive
Vaisberg (2019) [39]	Clinical trial	Brazil	NR	Probiotic added to whole dairy	IgA	Positive
Corsello (2017) [40]	Clinical trial	Italy	Both enrollment and follow-up: 2014-2015	Probiotic added to whole dairy	IgA	Positive
Lee (2017) [41]	Clinical trial	Korea	Enrollment: Mar and Dec 2016	Probiotic added to whole dairy	IgG	Positive
Nocerino (2017) [42]	Clinical trial	Italy	Both enrollment and follow-up: 2012	Probiotic added to whole dairy	IgA	Positive
Shida (2017) [43]	Clinical trial	Japan	Both enrollment and follow-up: 2012-2013	Probiotic added to whole dairy	IgA	Positive
Nagafuchi (2015) [29]	Clinical trial	Japan	Both enrollment and follow-up: 2010-2011	Probiotic added to whole dairy	Vaccine-specific response: Antibody titers, seroprotection rates IgA, IgG, IgM	Positive
Bosch (2012) [25]	Clinical trial	Spain	Both enrollment and follow-up: 2006-2007	Probiotic added to whole dairy	Vaccine-specific response: IgA, IgG	Positive
Lahtinen (2012) [44]	Clinical trial	Finland	NR	Probiotic added to whole dairy	IgA	Positive
Rizzardini (2012) [31]	Clinical trial	Italy	Enrollment: 2009 Follow-up: 2009	Probiotic added to whole dairy	Vaccine-specific response: IgA, IgG IgA, IgG, IgM Seroconversion rates: IgG	Positive
Snel (2011) [45]	Clinical trial	Netherlands	Both enrollment and follow-up: 2008	Probiotic added to whole dairy	IgE, IgG	Positive
Wassenberg (2011) [46]	Clinical trial	Switzerland	Enrollment: 2006-2007	Probiotic added to whole dairy	IgE, IgG	Positive

Koyama (2010) [47]	Clinical trial	Canada	Both enrollment and follow-up: Grass study (spring 2007); ragweed pollen study (summer-fall 2007)	Probiotic added to whole dairy	IgE, IgG, IgM	Positive
Perez (2010) [30]	Clinical trial	Argentina	Both enrollment and follow-up: 2006-2007	Probiotic added to whole dairy	Vaccine-specific response: Antibody titers IgA, IgD, IgG, IgM	Positive
Boge (2009) [24]	Clinical trial	France	Both enrollment and follow-up: Pilot study in 2005-2006; Confirmation study in 2006-2007	Probiotic added to whole dairy	Vaccine-specific response: Antibody titers, seroconversion rate, seroprotection rate	Positive
Kawase (2009) [48]	Clinical trial	Japan	Both enrollment and follow-up: 2006	Probiotic added to whole dairy	IgE	Positive
Martínez-Cañavate (2009) [49]	Clinical trial	Spain	NR	Probiotic added to whole dairy	IgA, IgE, IgG, IgM	Positive
Giovannini (2007) [50]	Clinical trial	Italy	Enrollment: 2003-2004 Follow-up: 2003-2005	Probiotic added to whole dairy	IgA, IgE, IgG, IgM	Positive
Olivares (2006) [51]	Clinical trial	Spain	NR	Probiotic added to whole diary	IgA, IgE, IgG	Positive
Spanhaak (1998) [52]	Clinical trial	Netherlands	NR	Probiotic added to whole dairy	IgA, IgD, IgE, IgG, IgM	Positive
Bumrungpert (2018) [53]	Clinical trial	Thailand	NR	Whey	IgG	Positive
Biesiekierski (2013) [54]	Clinical trial, crossover	Australia	Enrollment: Jan 2010-Jan 2011	Whey	IgA, IgG	Positive
Katayama (2011) [55]	Clinical trial	Japan	NR	Whey	IgA, IgG	Positive
King (2007) [33]	Clinical trial	United States	NR	Whey	Vaccine-specific response: Antibody titers	Positive
Micke (2001) [56]	Clinical trial	Germany	Both enrollment and follow-up: Aug 1998-Mar 1999	Whey	IgA, IgE, IgG, IgM	Positive

Wheeler (1997) [57]	Clinical trial, cross-over	United States	NR	Probiotic added to whole dairy	IgE	Positive
Shinohara (2020) [58]	Clinical trial	Japan	NR	Whole dairy: Milk	IgA	Neutral
Papacosta (2015) [59]	Clinical trial, cross-over	Cyprus	NR	Whole dairy: Milk	IgA	Neutral
Mangold (2012) [60]	Clinical trial	Austria	NR	Whole dairy: Fermented milk	IgA, IgD, IgE, IgG, IgM	Neutral
Yang (2012) [23]	Cohort	Taiwan	NR	Whole dairy: probiotic yogurt	IgA, IgE	Neutral
Morita (2006) [61]	Clinical trial	Japan	NR	Whole dairy: Fermented milk	IgE	Neutral
Siekmann (2003) [62]	Clinical trial	Kenya	Both enrollment and follow-up: Aug 1998-Aug 1999	Whole dairy: Milk	*H. pylori* IgA, IgG, IgM, tetanus IgG	Neutral
Pujol (2000) [63]	Clinical trial, cross-over	NR	NR	Whole dairy: Fermented milk	IgA, IgG, IgM	Neutral
Wheeler (1997) [32]	Clinical trial, cross-over	United States	NR	Whole dairy: Yogurt	Vaccine-specific response: Seroconversion rate IgA, IgE, IgG, IgM	Neutral
Link-Amster (1994) [64]	Clinical trial	Switzerland	NR	Whole dairy: Fermented milk	IgG	Neutral
Falth-Magnusson (1987) [65]	Clinical trial	Sweden	Enrollment: 1983-1984	Whole dairy: Milk	IgE	Neutral
Matthews (1974) [28]	Clinical trial	New Guinea	NR	Whole dairy: milk powder	Vaccine-specific response: IgG, Antibody titers IgM	Neutral
Zhang (2021) [66]	Clinical trial	China	NR	Probiotic added to whole diary	IgA, IgG, IgM	Neutral
Eden (2019) [67]	Clinical trial	Turkey	NR	Probiotic added to whole diary	IgA	Neutral
Yamamoto (2019) [68]	Clinical trial	Japan	Both enrollment and follow-up: Oct and Dec 2014	Probiotic added to whole dairy	IgA	Neutral
Zhang (2018) [69]	Clinical trial	China	NR	Probiotic added to whole dairy	IgA, IgG, IgM	Neutral

Yamamoto (2017) [70]	Clinical trial	Japan	Both enrollment and follow-up: 2013	Probiotic added to whole dairy	IgA	Neutral
Kabeerdoss (2011) [71]	Clinical trial	India	NR	Probiotic added to whole dairy	IgA	Neutral
Surono (2011) [72]	Clinical trial	Indonesia	NR	Probiotic added to whole dairy	IgA	Neutral
Hasegawa (2009) [73]	Clinical trial	Japan	Both enrollment and follow-up: 2008	Probiotic added to whole diary	IgE	Neutral
Ivory (2008) [74]	Clinical trial	United Kingdom	Both enrollment and follow-up: 2005-2006	Probiotic added to whole dairy	IgE, IgG	Neutral
Tiollier (2007) [75]	Clinical trial	France	NR	Probiotic added to whole dairy	IgA	Neutral
Xiao (2006) [76]	Clinical trial	Japan	Both enrollment and follow-up: 2004	Probiotic added to whole dairy	IgE	Neutral
De Vrese (2005) [26]	Clinical trial	Germany	NR	Probiotic added to whole dairy	Vaccine-specific response: IgA, IgG, antibody titers, seroprotection rate	Neutral
Ishida (2005) [77]	Clinical trial	Japan	Both enrollment and follow-up: 2002 and 2003	Probiotic added to whole dairy	IgE	Neutral
Ishida (2005) [78]	Clinical trial	Japan	Both enrollment and follow-up: 2002-2003	Probiotic added to whole diary	IgE	Neutral
Marteau (1997) [79]	Clinical trial	France	NR	Probiotic added to whole dairy	IgA, IgG, IgM	Neutral
Kaila (1992) [80]	Clinical trial	Finland	NR	Probiotic added to whole dairy	IgA, IgG, IgM	Neutral
Oda (2021) [81]	Clinical trial	Japan	Both enrollment and follow-up: 2017	Whey	IgA	Neutral
Lothian (2006) [82]	Clinical trial	Canada	Enrollment: Jan 2000-Jan 2002	Whey	IgE	Neutral
Rohr (2012) [83]	Clinical trial	China	NR	Casein	IgA, IgG, IgM	Neutral
Milewska-Wróbel (2020) [22]	Cross-sectional	Poland	NR	Dietary patterns: Maternal intake of yogurt, milk or cheese	IgE	Neutral
Keller (2014) [84]	Clinical trial	Germany	Both enrollment and follow-up: Mar and Oct 2011	Milk phospholipids	IgE	Neutral
Coman (2017) [21]	Clinical trial	Italy	NR	Probiotic added to whole dairy	IgA	Negative

Table 2. Consumption of Dairy Products/Components and Vaccine-Specific Immune Response After Vaccination (N=10)

Author (Year)	Study Population		Dairy Intervention Details	Vaccine Type and Timing of Administration	Vaccine-Specific IgG	Vaccine-Specific IgA or IgM	Antibody Titers	Seroprotection Rates or Seroconversion Rates
	N	Age and Health Status						
Whole Dairy Products								
Schaefer (2018) [27]	Intervention (milk powder): 10 Control (low isoflavone soy protein): 11	Elderly, hospitalized patients in retired centers and long-term care facilities	6 g milk powder twice a day for 8 weeks	Diphtheria, tetanus, and polio (DTaP) vaccine at week 4	NR	NR	Mean change in tetanus antibody level week 8-week 0: SS higher in intervention group (p=0.029) Mean post-vaccine tetanus antibody level at week 8: SS higher in intervention group (p=0.034) Diphtheria and pertussis antibody levels: NSS between groups	NR
Wheeler (1997) [32]	20 (cross-over trial of traditional yogurt and 2% milk)	Adults, atopic disease	8 oz traditional yogurt per day for 1 month (yogurt contained live, active *L. bulgaricus and S. thermophilus* at 2.5 to 3.0 x 10^8 per g and 3.5 to 4.1 x 10^8 per g) 8 oz milk twice daily for 1 month	Quadrivalent pneumococcal vaccine and the standard oral polio vaccine at study start (day 0)	NR	NR	NR	Mean number of patients with a response (ratio values of ≥3) to pneumococcal titers across 12 serotypes: NSS with the cross-over analysis

			1 month of one product, 2 weeks without dietary restrictions, 2-week washout period, 1 month of the other product	Quadrivalent pneumococcal vaccine and the standard oral polio vaccine at study start (day 0)				Mean number of patients with a response to polio vaccine (fold rise ≥2): NSS for polio 1, 2, or 3 with the cross-over analysis
Matthews (1974) [28]	Intervention (skim milk powder): 30 Control (no intervention): 24	Children, growth-retarded	Skim milk powder (25 g protein) 5 days per week for 8 months	Flagellin from *Salmonella adelaide* administered at 7 months	Total IgG antibody: Difference NSS between treatment groups at 2- or 6-weeks post-immunization	NR	Total antibody titers to flagellin: SS higher in the intervention group at 6 weeks post-immunization (p=0.002) NSS difference between groups at 2 weeks post-immunization	
Probiotics								
Nagafuchi (2015) [29]	Intervention (milk-based formula with prebiotics and probiotics): 12 Control (standard milk-based formula): 12	Elderly, Hospitalized	Formula administered enterally via percutaneous endoscopic gastrostomy for 14 weeks, no details on dose Intervention formula contains prebiotics bifidogenic growth stimulator (BGS) and galacto-oligosaccharides (GOS) and probiotics *L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus*	Influenza A/H1N1, A/H3N2, and B at week 4	NR	NR	Antibody titers A/H1N1: NSS differences between treatment groups at weeks 0, 4 (time of vaccination), 6, 8 or 12 A/H3N2: NSS differences between treatment groups at weeks 0, 4, 6, 8 or 12 B: SS lower in the intervention group vs. control at week 6 and 8 ($p < 0.05$); NSS difference at week 0,4,	

Bosch (2012) [25]	Intervention arm 1 (high-dose skim milk powder with probiotic): 19 Intervention arm 2 (low-dose skim milk powder with probiotic): 14 Control arm (placebo: skim milk powder): 15	Elderly, Hospitalized	High-dose: 5 x 10^9 cfu/day of *L. plantarum* CECT 7315/7316 in 20 g powdered skim milk for 3 months Low dose: 5 x 10^8 cfu/day of *L. plantarum* CECT 7315/7316 in 20 g powdered skim milk for 3 months	Influenza A/ H1N1, A/H3N2, and B 3-4 months prior to the intervention	Influenza-specific IgG: High-dose: SS increase post- vs. pre-intervention ($p = 0.023$) Low-dose and placebo: NSS difference pre- vs. post-intervention	Influenza-specific IgA: High-dose: SS increase post- vs pre-intervention ($p = 0.008$) Low dose: SS increase pre- vs. post-intervention ($p = 0.039$) Placebo: NSS difference pre- vs. post-intervention Influenza-specific IgM: NSS pre- vs. post-intervention for all treatment groups	NR	NR
Rizzardini (2012) [31]	4 intervention arms were evaluated with 2 treatment groups relevant to this review Intervention (probiotic drink): 56	Adults, healthy	One acidified dairy drink with *L. paracasei* ssp. *paracasei* (*L. casei* 431) once daily for 6 weeks. Minimum $1x10^9$ cfu/ dose	Influenza A/ H1N1, A/H3N2, and B at week 2	Changes from baseline, **plasma**: SS greater change in the intervention group vs. placebo for total IgG ($p=0.01$), IgG1 ($p<0.001$) and IgG3 ($p<0.001$) Changes from baseline, **salivary**: Difference NSS between treatment groups for total IgA or IgM Rate of substantial increase (≥2-fold increase), **salivary**:	Changes from baseline, **plasma**: NR Changes from baseline, **salivary**: Difference NSS between treatment groups for total IgA or IgM Rate of substantial increase (≥2-fold increase), **salivary**:	Rate of substantial increase (≥2-fold increase), **plasma**: Difference NSS between treatment groups for total IgG SS higher rate in the intervention group vs. control for IgG1 ($p<0.001$) and IgG3 ($p<0.001$)

	Control (placebo acidified dairy drink): 54				Rate of substantial increase (≥2 -fold increase), **salivary**: SS higher rate for IgA (p=0.035)	Difference NSS between treatment groups for total IgG or IgM		
Perez (2010) [30]	Intervention (Milk fermented with *S. thermophilus*, *L. acidophilus* CRL431, *L. casei* CRL730): 70 Control (Milk fermented with *S. thermophilus*): 70	Children, healthy	95 g milk bottle once daily for at least 4 months 95 x 10^8 cfu of *S. thermophilus*, 95 x 10^6 cfu of *L. acidophilus* and 95 x 10^6 cfu of *L. casei*	Diphtheria/ tetanus/ pertussis and *Haemophilus influenzae type B* (DTP-HiB) vaccine or 23-valent anti-pneumococcal vaccine, depending on age	NR	NR	Tetanus antibodies: Differences NSS between treatment and control for pre- and post-vaccination Pneumococcal antibodies: Differences NSS between treatment and control for pre- and post-vaccination	NR
Boge (2009) [24]	Intervention arm (dairy drink with probiotic): 44 pilot and 113 confirmatory Control arm (non-fermented dairy drink): 42 pilot and 109 confirmatory	Elderly, hospitalized patients and nursing home residents	2 bottles of 100 g dairy drink with *L. casei* DN-114 001 and traditional yogurt ferments per day for 7 weeks (pilot study) or 13 weeks (confirmatory study)	Influenza A/ H1N1, A/H3N2, and B at week 4	NR	NR	Confirmatory study: Geometric mean titers: Intervention group: SS increase for B at 3 weeks (p= 0.029), 6 weeks (p=0.027), and 9 weeks (p=0.025) after vaccination Differences NSS for A/H1N1 and A/H3N2 at 3, 6 and 9 weeks after vaccination	Confirmatory study: Seroconversion rate at 5 months after vaccination: SS increases in the intervention group vs. control for B (p=0.016) and A/H3N2 (p=0.031); NSS between treatment groups for A/ H1N1 Seroprotection rate at 3 weeks after vaccination: SS increase in the intervention group vs. control for

De Vrese (2005) [26]	Intervention arm 1 (*L. rhamnosus* GG): 22 Intervention arm 2 (*L. acidophilus* CRL431): 21 Control (placebo): 21	Adults, healthy	Whole dairy acidified milk product with *L. rhamnosus* GG or *L. acidophilus* CRL431 100 g/day (10^{10} cfu/serving) for 5 weeks for both intervention arms	Polio virus 1, 2 and 3 administered at day 8	Poliovirus serotype-specific IgG titer: Difference NSS between placebo and intervention groups for polio virus 1, 2 or 3	Poliovirus serotype-specific IgA titer: Polio 1=SS increase in intervention 1 vs. placebo (p=0.036); Difference NSS between intervention 2 and placebo Polio 2 and Polio 3=Difference NSS between placebo and intervention groups Poliovirus serotype-specific IgM titer: Polio 2=SS increase in intervention 2 vs. placebo (p=0.040); Difference NSS between intervention 1and placebo	Control group: Differences NSS for all 3 strains at 3, 6, and 9 weeks after vaccination Pilot study: NSS for all 3 strains at 3 weeks after vaccination in all treatment groups	Δ Neutralizing antibodies titer: Polio 1=SS increase in intervention 1 vs. placebo (p=0.048); NSS difference between placebo and intervention 2 Polio 2=SS increase in intervention 1 vs. placebo (p=0.014); NSS difference between placebo and intervention 2 Polio 3=SS increase in intervention 2 vs. placebo (p=0.011); NSS difference between placebo and intervention 1 Δ PoBI Titer: NSS difference between placebo and intervention groups for polio 1, 2, or 3	Differences NSS in seroprotection rates between placebo and intervention groups for A/H1N1 strain (p=0.045); NSS between treatment grups for B and A/H3N1 Pilot study: NSS for seroprotection or seroconversion rates at 3 weeks after vaccination in all treatment groups

						Polio 1 and Polio 3= Difference NSS between placebo and intervention groups		
Dairy Proteins								
King (2007) [33]	Intervention arm (Similac with Fe formula, 850 mg/L bovine lactoferrin): 26 Control arm (Similac with Fe formula, 102 mg/L bovine lactoferrin): 26	Infants ≤4 weeks of age, healthy	Similac iron formula with bovine lactoferrin	Diphtheria and tetanus (DT), *Haemophilus influenzae type B (HiB)*, and hepatitis B, according to the standard schedule	NR	NR	Mean antibody levels at 9 months: Diphtheria, tetanus, *Haemophilus influenzae type B*, and hepatitis B: treatment vs. control NSS Mean antibody levels at 12 months: Hepatitis B: treatment vs. control NSS	NR

SS: Statistically significant ($p<0.05$)

NSS: Not statistically significant ($p\geq0.05$)

Discussion

This review provides a systematic assessment of the epidemiologic literature regarding dairy products/components' potential impacts on the immune response to vaccination. The potential impacts of dairy products/components on immunoglobulins are also described in this review. Among various populations, dairy interventions were observed to modify the adaptive immune response after vaccination with significantly increased levels of IgA and IgG, vaccine-specific antibody titers, seroconversion rates, and seroprotection rates. The evidence describing the benefits of dairy seems to be most consistent for probiotics added to whole dairy products. Three randomized, double-blind, placebo-controlled trials reported enhanced productions of influenza vaccine-specific antibodies with *Lactobacillus* probiotic supplementation in dairy drinks/milk powder [24,25,31]. Significant increases in seroprotection/seroconversion were reported in 2 trials that collected this information [24,31]. Sporadic changes in polio-specific antibodies were also observed with *Lactobacillus* supplementation, although no differences in the number of patients with seroprotection were found [26]. Vaccination is an important preventative measure to protect against infections and reduce the severity/duration of illness [34]. Currently, the COVID-19 pandemic is on-going and overlaps with influenza and respiratory syncytial virus seasons. In this era of 'tripledemic', our study suggests that dairy products and their components could be an effective vehicle to enhance the efficacy of vaccines.

Our findings on the potential immune benefits from probiotics in dairy are consistent with clinical trials evaluating vaccine efficacy and probiotics given without dairy [35]. Probiotics may be the bioactive component of dairy products that confer an immunological benefit. Research is ongoing on the physiological effects of probiotics; the mechanism may include the stimulation of the innate immune response in the gut and/or the interaction of probiotic bacteria with immune and intestinal epithelial cells [36]. Dairy products may be an ideal vehicle to deliver probiotics, as they are a well-accepted food item and provide additional valuable nutrients such as vitamin D and calcium.

In this review, the critical appraisal of the included studies indicates that the evidence base is strong, with the inclusion of 60 positive or neutral quality studies. Another strength of this review is that we followed all standard PRISMA recommendations for systematic reviews throughout the entirety of study conduct. Additionally, as the scope of the review was broad, this review is comprehensive and has captured the totality of the published literature on dairy and non-inflammatory immune response with or without vaccinations.

While this review suggests a beneficial role for dairy in the immune response to vaccination, the interpretation of these findings is impacted by substantial heterogeneity in study features, including the exposure under study, exposure dose/duration, the probiotic strain under investigation, the vaccine type, the age and comorbidities of the study population, and the different biological matrices used to measure immunoglobulins (including serum, saliva, and fecal matter). Variability was also observed in the timing of the dairy intervention and vaccine administration, with vaccines being given at the beginning of the study period or during the dairy intervention. Probiotics evaluated in the included studies comprised various species and strains, both naturally occurring and experimental. It is possible that probiotics' immune-modulating effect is strain-specific and, thus, the positive or negative findings may be related to strain-specific variation. Due to the heterogeneity in exposures and outcomes, quantitative synthesis was not advisable. Finally, the interpretation of immunoglobulin results remains challenging as clinical relevance was not evaluated in the included studies. Specifically, the evidence connecting enhanced antibody productions by dairy interventions to protections against disease incidence and/or severity of

illness was not available in the included studies. In tandem to the current review, we identified another evidence base related to the influence of dairy products/components on infectious disease incidence and the duration/severity of disease. This topic will be evaluated in a separate publication, and the conclusions of that companion paper will inform the current review.

Notably, this review highlights the evidence gaps and provides a potential roadmap for additional research on dairy and immune response. Multicenter, randomized, placebo-controlled trials or prospective cohort studies may be beneficial. These studies should include a range of specified exposure durations/doses, focused probiotic strains/dairy proteins, and clinically relevant outcomes (i.e., disease incidence). Study design with longitudinal measures of immunoglobulins and vaccine-specific immune response are also needed to fill the evidence gaps. Studies should incorporate a period of follow-up to obtain disease incidence and measures of immune response. Additional studies may also consider probiotic supplementation in dairy among the pediatric populations, where vaccination is routine and dairy products are recommended in the dietary guidelines [4,5].

Conclusions

The consumption of dairy products/components prior to and after vaccination could represent an effective intervention to improve the antibody response to vaccination. This intervention could potentially provide a public health benefit by enhancing vaccine efficacy and thereby increasing protections of individuals susceptible to severe illness from vaccine-preventable diseases.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by MS and MM. The first draft of the manuscript was written by MS and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

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