Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

The influence of probiotics on vaccine responses – A systematic review

Petra Zimmermann *, Nigel Curtis

Department of Paediatrics, The University of Melbourne, Parkville, Australia
Infectious Diseases Unit, The Royal Children's Hospital Melbourne, Parkville, Australia
Infectious Diseases & Microbiology Research Group, Murdoch Children's Research Institute, Parkville, Australia

ARTICLE INFO

Article history:
Received 2 April 2017
Received in revised form 22 August 2017
Accepted 24 August 2017
Available online xxxx

Keywords:
Lactobacillus
Bifidobacteria
Antibodies
Immunoglobulin
Microbiota
Microbiome
Titer

ABSTRACT

The immunomodulatory effects of probiotics offer a relatively cheap means to improve vaccine efficacy and duration of protection. We systematically reviewed prospective randomised placebo-controlled studies in humans that have investigated the influence of probiotics on humoral vaccine responses.

We found 26 studies, involving 3812 participants, investigating the use of 40 different probiotic strains on the efficacy of 17 different vaccines. A beneficial effect of probiotics was reported in about half of the studies. The evidence for a beneficial effect of probiotics on vaccine response was strongest for oral vaccinations and for parenteral influenza vaccination. However, there was substantial variation between studies in the choice of probiotics, strain, dose, viability, purity, and duration and timing of administration. The one study that investigated the effect of probiotics administration to mothers during pregnancy found lower vaccine response in infants.

Probiotics offer a relatively cheap intervention to improve vaccine efficacy and duration of protection. There is sufficient evidence from the studies in our review to suggest this strategy is worth pursuing. However, future studies should focus on establishing optimal strains, doses and timing of administration in relation to vaccination.

Contents

1. Introduction

The immune response to vaccinations varies substantially between individuals. This has implications for both protective efficacy and duration of protection. Factors contributing to the

* Corresponding author at: The Royal Children's Hospital Melbourne, 50 Flemington Road, Parkville, 3052, Australia.
E-mail address: petra.zimmermann@rch.org.au (P. Zimmermann).

http://dx.doi.org/10.1016/j.vaccine.2017.08.069
0264-410X/

Please cite this article in press as: Zimmermann P, Curtis N. The influence of probiotics on vaccine responses – A systematic review. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.08.069

variation in vaccine responses include age [1–3], gender [4], genetics [5–7], geographic location [8], time of day vaccine administered [9], and co-administered vaccines [10,11].

In recent years, considerable research has revealed the importance of the intestinal microbiota in the development of the immune system and regulation of immune responses [12,13]. While there have been only few studies on the effect of the intestinal microbiota on vaccine responses [14–18], many studies have investigated the effect of concurrent administration of probiotics around the time of vaccination.

Probiotics are defined as live microorgansims which, when administered orally in adequate amounts (thought to be $\geq 1 \times 10^9$ colony forming units (CFU) daily), are beneficial to the host. [19] The most frequently used microorgansims are *Lactobacillus spp*, *Bifidobacterium spp,* and *Saccharomyces boulardii.* The mechanism of action of probiotics include normalisation of perturbed microbiota, regulation of intestinal transit, increased turnover of enterocytes, gut barrier reinforcement, colonisation resistance, acid and short-chain fatty acid production, vitamin synthesis, and bile salt metabolism [19]. Probiotics enhance both innate and adaptive immunity [20,21], and have been found to be beneficial in treatment of acute gastroenteritis [22,23], in prevention of antibiotic-associated diarrhoea [24], in reduction of infection in children attending day care centres [25–27], and in prevention of eczema and allergies [28,29]. However, most studies investigating the influence of probiotics on the immune response in humans have been small in size or limited. Despite this, there has been an explosion in the use of probiotics, promoted by the pharmaceutical industry; the global probiotics market size exceeded US$35 billion in 2015. An evidence base to guide interventions is critically needed. Here, we systematically review studies investigating the influence of probiotics on vaccine responses.

2. Literature review

In April 2017, MEDLINE (1946 to present) and Embase (1947 to present) were searched using the Ovid interface with the following search terms: (probiotics OR *Lactobacillus* OR *Bifidobacterium*) AND (vaccin* OR immun* OR antibod* OR humoral) without any language limitations. This identified 2366 studies. Of these, 25 fulfilled our inclusion criteria of prospective randomised placebo-controlled studies in humans measuring humoral vaccines responses in plasma or stool after administration of probiotics. References were hand-searched for additional publications and 1 further relevant study was found (Fig. 1). A p-value ≤ 0.05 was used to define statistically significant findings.

3. Results

A total of 26 studies were reviewed, involving 3812 participants, investigating the use of 40 different probiotic strains on the efficacy of 17 different vaccines (DTP (2), DTwP, DTaP-Hib (2), DTaP-IPV-Hib (2), HAV, HBV (2), Hib, LAIV, MMRV, OCV (2), OPV, ORV, PCV7, PPV23 (2), Polio, TIV (11), Ty21a). The dose of probiotic used in each study varied between 10^8 and 10^{13} colony forming units CFU per day.

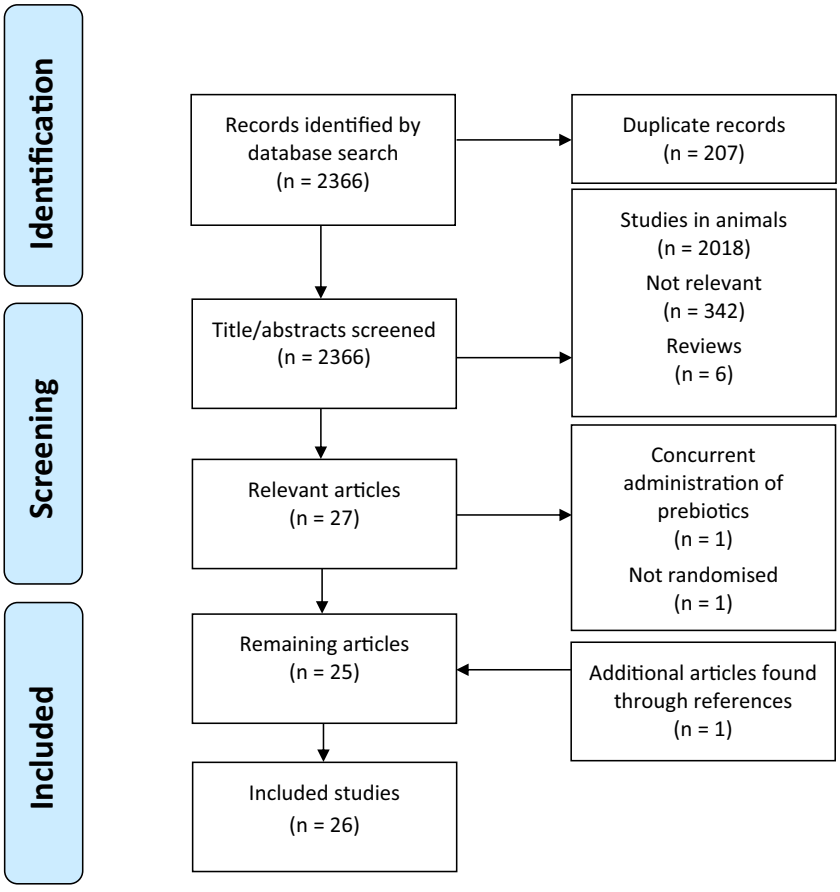

Fig. 1. Flow diagram of selection of articles included in the review.

Please cite this article in press as: Zimmermann P, Curtis N. The influence of probiotics on vaccine responses – A systematic review. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.08.069