Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Review

The influence of the intestinal microbiome on vaccine responses ☆

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ARTICLE INFO

Article history:
Received 13 June 2017
Received in revised form 11 April 2018
Accepted 20 April 2018
Available online xxxx

Keywords:
Microbiota
Stool
Intestine
Sequencing
16S rRNA
Vaccination
Immunisation
Immunity

ABSTRACT

There is substantial variation between individuals in the immune response to vaccinations. The intestinal microbiome plays a crucial rule in the development and regulation of the immune system and therefore its composition might affect how individuals respond to vaccinations. In this review, we summarise studies that investigated the influence of the intestinal microbiome on humoral and cellular vaccine responses.

To date, only four studies (three in infants and one in adults) have investigated the influence of the intestinal microbiome on vaccine responses. All found an association between the intestinal microbiome and vaccine responses. Despite the heterogeneity in study designs (including different vaccines, schedules, timing of collection of stool and blood samples, analysis methods and reporting of results on different taxonomic levels), findings across studies were consistent: a higher relative abundance of the phylum Actinobacteria (oral and parenteral vaccines) and Firmicutes (oral vaccines) was associated with both higher humoral and higher cellular vaccine responses, while a higher relative abundance of the phylum Proteobacteria (oral and parenteral vaccines) and Bacteroidetes (oral vaccines) was associated with lower responses.

Further, well-designed, adequately powered studies using whole-genome sequencing (to include the influence of viruses, fungi and parasites) are needed to investigate in more detail the influence of the intestinal microbiome on vaccine responses. This will help identify strategies to improve vaccine efficacy and duration of protection, particularly in infancy when the intestinal microbiome is more amenable to external influences and plays an important role in the development of the immune system.

Contents

☆ **Once sentence summary:** The relative abundance of certain bacterial taxa in the intestinal microbiome influences both humoral and cellular immune responses to oral and parenteral vaccines.

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https://doi.org/10.1016/j.vaccine.2018.04.066
0264-410X/

1. Introduction

There is substantial variation between individuals in the immune response to vaccinations. The serological response to hepatitis B vaccine, for example, varies more than 100-fold at seven months of age and some infants do not have any measurable antibodies [1,2]. Similarly, the response to pneumococcal and Hib vaccination at six months of age varies up to 40-fold [1]. This has implications for both protective efficacy and duration of protection. Factors contributing to the variation in vaccine response include age [3–5], gender [6], genetics [7–9], geographic location [10], time of day vaccine administered [11] and co-administered vaccines [12,13]. A further important factor which likely influences vaccine responses is the intestinal microbiome.

In recent years, considerable research has revealed the importance of the intestinal microbiome in the development of the immune system and regulation of immune responses [14,15]. Abundance of certain bacteria in the intestinal microbiome have been linked to susceptibility to neonatal sepsis [16], chronic inflammatory bowel disease [17], chronic obstructive pulmonary disease [18], diabetes mellitus [19], and eczema, allergies and asthma [20]. Advances in DNA sequencing technology and bioinformatic analysis have facilitated the ability to determine differences in the composition of the intestinal microbiome. Despite the evidence for the intimate relationship between the intestinal microbiome and the immune system, only a limited numbers of studies have investigated the effect of the composition of the intestinal microbiome on vaccine responses. These studies are summarised in this review.

2. Systematic review methods

In April 2017, MEDLINE (1946 to present) and Embase (1947 to present) were searched using the Ovid interface with the following search terms: (microbiome OR microbiota OR biodiversity OR Actinobacteria OR bacteroides OR *Bifidobacterium* OR *Enterobacteriaceae* OR *lactobacillus* OR Proteobacteria) AND (feces OR faeces OR meconium OR intestin* OR) AND (RNA, ribosomal OR sequence analysis, DNA OR culture or quantif*) AND (vaccin* OR immuniz* OR immunis* OR antibodies OR immunoglobulin OR immunity, humoral OR immunity, cellular OR mucosal immunity) without any language limitations. This identified 757 and 1062 studies, respectively. Of these, four fulfilled our inclusion criteria of studies in humans investigating the influence of the composition of the intestinal microbiome on humoral or cellular vaccines responses, in which no concomitant probiotics were given. References were hand-searched for additional publications and no further relevant studies were found.

3. Systematic review results

Three studies reporting results from 146 infants (206 stool samples) and one study reporting results from 17 adults (170 stool samples) met the inclusion criteria (Table 1). Two of the studies were done in developing countries [21,22]. Responses to oral vaccinations were investigated in two studies [22,23], to parenteral vaccination in one [24], and to both oral and parenteral in one [21]. Two studies measured humoral and cellular responses in serum [21,23], while one study each measured humoral responses in serum [22] or in stool [24]. Multiple methods were used to determine the intestinal microbiome, including bacterial culture [24], PCR for Bifidobacteria [21,24], Human Intestinal Tract Chip microarray [22], and 16S rRNA gene sequencing (Roche 454 [23] Illumina MiSeq [21]). An overview of the associations between the intestinal microbiome and vaccine responses is provided in Table 2.

3.1. Oral vaccination

Three studies investigated the influence of the intestinal microbiome on the immune response to oral vaccines; two of these were done in infants [21,22] and one in adults [23].

The first study compared the intestinal microbiome of infants in Ghana, using 39 participants who were responders to oral rotavirus vaccination (defined as serum rotavirus-specific immunoglobulin (Ig) A levels $\geq$ 20 IU/ml measured four weeks after the third vaccine dose) with 39 who were non-responders. The study found that responders had an increased relative abundance of *Streptococcus gallolyticus*, a decreased relative abundance of the phylum Bacteroidetes, and a higher Enterobacteria-*Bacteroides* ratio in their stools taken at 6 weeks of age (two weeks before the third vaccine dose). The study did not find a difference in the diversity of the intestinal microbiome between responders and non-responders [22].

The second study, investigated the influence of the intestinal microbiome on the immune response to oral poliovirus vaccination in 48 infants in Bangladesh. A higher relative abundance of the phylum Actinobacteria (families *Coriobacteriaceae* and *Bifidobacteriaceae* (species *Bifidobacterium longum* subspecies *infantis* and *B. longum* subspecies *longum*)) at the age of 15 weeks was associated with higher polio-specific T cell responses and IgG levels in serum at the same time points (one week after the fourth vaccine dose). In contrast, a higher relative abundance of the order Pseudomonadales was negatively associated with polio-specific T cell responses and IgG levels in serum [21].

The third study, investigated the influence of the intestinal microbiome on the immune response to oral *Salmonella* Typhi vaccination in 17 adults in the US one week before receiving the vaccine until two months after. The study found that participants with an overall more diverse, complex bacterial communities (mostly consisting of the order Clostridiales, predominantly the families *Lachnospiraceae* and *Ruminococcaceae*) had multiphasic cell-mediated immune responses, which is associated with a better response to the oral *Salmonella* Typhi vaccination. The study did not find differences in overall community diversity between humoral responders and non-responders (measured by serum typhoid-specific IgA and IgG levels). All the measurements were made within two months of administering the vaccine [23].

3.2. Parenteral vaccination

Two studies in infants investigated the influence of the intestinal microbiome on the immune response to intramuscular vaccination [21,24]. The first, investigating 20 infants in France, measured faecal polio-specific IgA levels after intramuscular vaccination with a pentavalent diphtheria-tetanus-acellular pertussis-

Please cite this article in press as: Zimmermann P, Curtis N. The influence of the intestinal microbiome on vaccine responses. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.04.066