Types of acute phase reactants and their importance in vaccination (Review)

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Abstract. Vaccines are considered to be one of the most cost-effective life-saving interventions in human history. The body's inflammatory response to vaccines has both desired effects (immune response), undesired effects [(acute phase reactions (APRs)] and trade-offs. Trade-offs are more potent immune responses which may be potentially difficult to separate from potent acute phase reactions. Thus, studying acute phase proteins (APPs) during vaccination may aid our understanding of APRs and homeostatic changes which can result from inflammatory responses. Depending on the severity of the response in humans, these reactions can be classified as major, moderate or minor. In this review, types of APPs and their importance in vaccination will be discussed.

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1. Introduction

The association between the strength of the acute phase response and vaccination efficacy is of key importance to human and veterinary medicine. Proteins which are expressed in the acute phase are potential biomarkers for the diagnosis of inflammatory disease, for example, acute phase proteins (APPs) are indicators of successful organ transplantation and can be used to predict the ameliorative effect of cancer therapy (1,2). APPs are primarily synthesized in hepatocytes. The acute phase response is a spontaneous reaction triggered by disrupted homeostasis resulting from environmental disturbances (3). Acute phase reactions (APRs) usually stabilize quickly, after recovering from a disruption to homeostasis within a few days to weeks; however, APPs expression levels often remain elevated in long lasting infection and chronic disease states, such as cancer (4-6).

Classification of acute phase reactions is dependent on the change in APP concentration: A 10-100-fold elevation is considered major; a 2-10-fold elevation is considered moderate; and a less than 2-fold elevation is considered minor (7). The APPs elevated in a major APR include C-reactive protein (CRP) and serum amyloid (SA); the APPs elevated in a moderate APR include α1-acid glycoprotein (AGP); and the APPs elevated in a minor APR include fibrinogen, haptoglobin (Hp) and ceruloplasmin (Cp) (8).

In response to infection, the liver synthesizes a large quantity of APPs (8). There are 8 proteins which are overexpressed in APRs denoted as 'positive' APPs, including Hp, SA, fibrinogen, Cp, AGP, α-1 antitrypsin (AAT), lactoferrin (Lf) and CRP. Similarly, there are a number of 'negative' APPs the expression levels of which are reduced, including albumin, transferrin and transthyretin (8).

The APP is elicited by cytokines, including those functioning as positive and negative growth factors and cytokines with proinflammatory or anti-inflammatory activity. Positive or negative growth factor cytokines involved include: Interleukin (IL)-2; IL-3; IL-4; IL-7; IL-10; IL-11; IL-12; and granulocyte-macrophage colony stimulating factor (9). Proinflammatory cytokines involved include tumour necrosis factor (TNF)-α/β; IL-1α/β; IL-6; IFN-α/γ; IL-8; and macrophage inhibitory protein-1 (6). Cytokines involved in the anti-inflammatory response include: IL-1 receptor antagonists; soluble IL-1 receptors; IL-1 binding protein; and TNF-α binding protein. Table I shows acute phase reactants associated, inflammatory cytokines and references.

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2. Inflammation and APPs

The acute inflammatory reaction is an essential immune response required for vaccinations to initiate temporary simulated immunity. The innate response is the first branch of the immune system stimulated by invading pathogens, should they cross the body's anatomical and chemical barriers. The innate immune system is also activated by APP synthesis as these molecules mediate inflammation.

After vaccination, pro-inflammatory cells are activated and produce cytokines which diffuse into the extracellular fluid and circulate in the blood. In response, the liver upregulates the synthesis of APPs, preceding the specific immune reaction within a few hours. Monitoring APP expression levels may be an indicator of efficacy of a vaccine in stimulating the innate immune system and may be a useful biomarker in the future development of vaccines.

3. Types of APPs

C-reactive protein (CRP). CRP is a member of the short evolutionarily conserved pentraxin group of plasma proteins, consisting of 5 identical non-glycosylated peptide subunits which link to form a cyclic pentamer structure (10,11). CRP is produced as a result of pro-inflammatory cytokine signaling primarily mediated by neutrophils and monocytes. CRP concentration is elevated during infection or inflammation as part of the innate immune response and alteration of CRP plasma concentration is dependent on the rate of CRP synthesis and the severity of infection (10). The half-life of CRP in plasma is ~19 h and is cleared by the urinary system (10,12) and CRP stimulates immune cells by binding to Fcγ receptors (FcγR) on leukocytes (monocytes, neutrophils and cells of a myeloid lineage) and increases production of IgG, linking the innate and adaptive immune systems (13). CRP-FcγR binding also facilitates the anti-inflammatory responses (14).

It has been proposed that CRP may have value as a diagnostic marker for active inflammation and infection. IL-6, IL-1 and TNF-α trigger hepatocyte mediated synthesis of CRP in response to active infection or inflammation. Subsequently, CRP binding to bacterial polysaccharides in the presence of calcium activates downstream compliment pathways and ultimately results in phagocytosis (15,16); however, the primary function of CRP is to recognize foreign pathogens and components of damaged cells through binding to phosphocholine (PC), a terminal head group of the lipoteichoic acid which is a component of the cell walls of certain Gram positive bacteria and a component of the mammalian cell membrane. In normal healthy cells, phosphocholine is not exposed however, when cells are damaged or are dying, CRP is able to bind to the PC present on the cell membrane (17). In addition, CRP promotes complement fixation, binding to phagocytized cells and triggers the elimination of cells targeted by the inflammatory response pathway (17-19). There is a direct association between the elevated levels of CRP and the risk of coronary artery and cerebrovascular thrombosis interfering with endothelial nitric oxide (NO) bioavailability, by decreasing endothelial NO synthase expression and increasing the production of reactive oxygen species (20,21).

In the USA, CRP levels in patients tend to be higher in females compared with males in healthy humans (2.7 vs. 1.6 mg/l, respectively) and these levels are exacerbated with age, for example one study reported CRP levels of 1.4 mg/l between the ages of 20-29 vs. 2.7 mg/l in those over 80 (22). Meanwhile, ethnicity has little effect on CRP levels (22).

When CRP was studied in non-human species, rabbits served as the primary experimental model due to their susceptibility to infection and the similarity of pathogenesis to what is observed in humans, rabbit CRP behaves more similar to human CRP compared with rat CRP in terms of its dynamic changes during acute phase response (13,23).

Haptoglobin (Hp). Hp is a glycoprotein synthesized in the liver and present in serum at concentrations of 3-30 μmol/l. Serum levels of Hp increase 3-8-fold in response to inflammation and injury and Hp is eliminated from the plasma in 3-5 days (24,25). Hp binds free hemoglobin (Hb) for detoxification and Hb is highly toxic due to its heme group which mediates the generation of hydroxyl radicals (24). The elimination of Hb and its iron constituent occurs by the formation of a noncovalent Hb-Hp complex which is released into the blood by intravascular hemolysis and subsequently removed by reticuloendothelial receptor-mediated endocytosis and tissue macrophages via interacting with CD163 cell-surface receptor (26). Free hemoglobin is very toxic to the human body due to its ability to bind NO which is a key modulator of vascular tone (27). Hp mediated NO binding prevents NO activity in vascular smooth muscle cells resulting in changes to vasomotor constriction, potentially causing endothelial damage which may contribute to cardiovascular disease, and pulmonary and systemic hypertension (28).

Hp has several functions in the cellular and humoral aspects of the innate and adaptive immune systems (24), including inhibiting prostaglandin production, enhancing the antibody production, leukocyte recruitment and migration, modulation of cytokine release, which are the regulatory mediators secreted by T cells and other immunoactive cells following an injury, infection and tissue repair (29-31). Conditions associated with a reduction or absence of Hp, such as hypohaptoglobinemia or ahaptoglobinemia, result in severe allergies involving the skin, lungs and anaphylaxis (29-31). Hp also suppresses T cell proliferation, including Th2 and Th4 cytokines synthesis (32), and cyclooxygenase and lipoxygenase activity, thus contributing to the regulation of the immune response to potentially damaging inflammation or infection (33).

Serum amyloid A (SAA). SAA is an APP and a apolipoprotein, which binds to high-density lipoproteins (HDL) in the plasma, During an APR, the fraction of apoA1 in HDL falls while that of SAA rises, becoming the predominant apolipoprotein (apo SAA), exceeding apo A-1 (the major apolipoprotein of native HDL) and reduces the effectiveness of HDL recycling cholesterol to the liver during inflammation (34). SAA displaces apolipoprotein A-1 from HDL, and becomes the predominant circulating HDL3 apolipoprotein mediating reverse cholesterol transport and inhibiting the LDL oxidation. LDL oxidation promotes foam cell formation, and thus, this reduces the risk of atherosclerosis (27). SAA is found at concentrations of 40 ug/ml in healthy males in the UK (34). During acute infection, SAA plasma levels are elevated by up to 1,000-fold (34).

Table I. Acute phase reactants, associated inflammatory cytokines and references.

A, Positive acute phase reactants

Author, year	Reactant	Associated cytokines	(Refs.)
Sharpe-Timms *et al*, 2010	Haptoglobin	IL1β, IL-6, IL-8, TNF-α,	(9)
He *et al*, 2006	Serum amyloid	IL1β, IL-6, IL-8, IL-12, IL-23	(143)
Lu *et al*, 2015	Fibrinogen	IL-6, IL-6, TNF-α, IL-1β, IL-8	(144)
Lazzaro *et al*, 2014	Ceruloplasmin	IL-1β, TNF-α, IFN-1	(145)
Martinez Cordero *et al*, 2008	α-1 acid glycoprotein	TNF-α, IL-1, IL-6	(146)
de Serres and Blanco, 2014	α-1 antitrypsin	TNF-α, IL-6, IL-1β, IL-8, IL-32	(147)
Haversen *et al*, 2002	Lactoferrin	TNF-α, IL-6, IL-1β, IL-8	(148)
Du Clos, 2000	C-reactive protein	IL-6, IL-1a, IL-1β, TNF-α	(149)

B, Negative acute phase reactants

Author, year	Reactant	Associated cytokines	(Refs.)
Spadaro *et al*, 2014	Albumin	IL-6, TNF-α	(150)
Feelders *et al*, 1998	Transferrin	IL-6, TNF-α, IL1	(151)
Bartalena *et al*, 1992	Transthyretin	IL-6, IL-1, TNF-α	(152)

IL, interleukin; TNF, tumor necrosis factor.

SAA has been shown to be an efficient carrier of retinol during an infection, while retinol is important for promotion and maturation of innate immune cells, expression of retinol transporter is reduced during infection, providing insight into the underlying mechanisms involved in the redirection of retinol in response to infection compensating to the markedly reduced levels of serum retinol binding protein transporter following a microbial infection (35). During inflammation, macrophages and monocytes present at the inflammatory site release cytokines, such as IL-6, initiating the induction of SAA synthesis and release of SAA by the liver into the plasma (16).

SAA is a conserved protein which circulates in the plasma and is able to bind to surface ligands of microbial pathogens in a calcium-dependent manner (36). SAA binds to microbial polysaccharides, which are part of the cell wall of gram-negative bacteria, and matrix components via carbohydrate determinant links, including heparin, 6-phosphorylated mannose, 3-sulfated saccharides and the 4,6-cyclic pyruvate acetal of galactose (37,38). SAA binds to apoptotic and necrotic cells facilitating its clearance *in vivo* (39).

Most species possess two main acute phase apo SAA isoforms of hepatic origin in their serum, SAA1 and SAA2 are APPs with the ability to form amyloid proteins *in vivo* and SAA1 and SAA2 represent multiple allelic forms which are alternatively expressed by three different genes in humans (40). SAA4 is constitutively expressed across a number of tissues and has been shown to form amyloid when mutated (41). SAA1a is frequently present in amyloid fibrils and is possibly the most amyloidogenic form of SAA1. Although the majority of SAA1 and SAA2 are found bound to HDL, they are only a minor protein component in a healthy state. This classification helps differentiate between regulated acute phase reactants of hepatic origin or constitutive proteins (42).

Fibrinogen. Fibrinogen is an important protein involved in blood clotting, homeostasis, inflammation and tissue repair. Fibrinogen is a 340-kDa soluble glycoprotein found in the blood, and a major component of fibrin which is synthesized in the liver. In healthy adults, fibrinogen plasma levels are ~150-400 mg/dl, and during infection, expression levels of fibrinogen can increase by ≤20-fold (43). At a site of injury, fibrinogen facilitates aggregation of activated platelets through binding to glycoprotein IIb/IIIa cell surface receptor (43), triggering platelet adhesion, and subsequently, thrombin cleaves fibrinogen into fibrin monomers which polymerize to form a clot (44,45) and are stabilized by activated factor XIII (46). The strength of the fibrin clot is influenced by the concentration of fibrinogen (44). A structural scaffold is formed by the fibrin clot onto which leukocyte platelets and fibroblasts adhere and infiltrate the injury site. Extravascular plasma generates thrombin which ultimately leads to deposition of fibrinogen (47), therefore injury, infection and auto-immunity are associated with extravascular fibrinogen (48,49).

Ceruloplasmin (Cp). Cp is a major copper transport protein present in the plasma and is produced by the hepatic parenchymal cells (50). Human Cp (hCp) is a 132 kDa α2-globulin which can bind up to six copper ions, and serum concentration levels in healthy individuals are ~0.2-0.6 mg/ml, which increases >2-fold during inflammation (51). Overall, ~95% of serum copper is bound to Cp (52). hCp has ferroxidase activity and functions in the mobilization of iron for transport by

oxidizing Fe^{2+} to the less reactive Fe^{3+} and incorporating Fe^{3+} into apotransferrin (53). This oxidation prevents the formation of reactive oxygen species and toxic products of iron (54,55). Therefore, Cp has an essential role in iron metabolism and the elimination of free iron (56-58). Cp is an APR and Cp expression levels increase during infection, stress and inflammation (59). Cp also possesses antioxidant properties and functions in the removal of free radicals such as H_2O_2 during wound healing, collagen formation and the maturation phase which brings about extracellular matrix remodeling and resolution of the granulation of tissue (60,61). However, studies have shown that Cp can also act as a pro-oxidant by promoting the oxidation of low density lipoprotein (62,63).

α1-acid glycoprotein (AGP). AGP is an APR which stabilizes the biological activity of plasminogen activator inhibitor-1, preventing platelet aggregation (64), and is present in the plasma of healthy humans at concentrations of 0.6-1.2 mg/ml (65). However, these expression levels increase 2-7-fold during an APR (53,66). AGP expression in the liver is induced by activation of IL-1β, IL-6 and TNF-α, and is inhibited by growth hormone (67,68). AGP is considered a natural anti-inflammatory agent with respect to its anti-neutrophilic activity. For example, AGP modulates neutrophil chemotactic migration and superoxide generation in a concentration-dependent manner assisting in the re-establishment of systemic homeostasis following an infection (59,69,70). AGP also inhibits monocyte chemotaxis and cellular leakage caused by histamine and bradykinin levels which are reduced by AGP, and additionally, AGP reduced the synthesis of soluble TNFα receptor leading to an inhibition of the inflammatory process (70). Meanwhile, AGP induces IL-1 receptor antagonism expressed on peripheral blood monocytes (71-73).

α-1 antitrypsin (AAT). AAT is the most abundant serine protease inhibitor in human blood (65). AAT is present in bodily fluids, including the saliva, tears, urine, bile and circulating blood. AAT consists of a single polypeptide chain made of 394 amino acid residues containing one free cysteine residue and three asparagine-linked carbohydrate side-chains. AAT aids in the elimination of acute inflammation, tissue proteolytic damage by neutrophil elastase in the lungs and inhibits lipopolysaccharides and the release of inflammatory mediators such as TNF-α and IL-1β (65,74,75). AAT is synthesized in the liver but is also produced by other blood cells such as monocytes, macrophages, pulmonary alveolar cells and by intestinal and corneal epithelium (65,74,75). Synthesis of AAT occurs at a rate of 34 mg/kg and the protein clearance rate (half-life) is 3-5 days. As a result, high plasma concentrations of AAT usually range from 0.9-2 mg/ml in healthy individuals (76-80). During an inflammatory response, local AAT synthesis results in the invasion of inflammatory cells followed by an acute rise in AAT expression levels by as much as 11-fold (81).

Lactoferrin (Lf). Lf is a multifunctional 80 kDa glycoprotein which binds to Fe^{3+} and an innate immunity factor present in a range of secretory fluids, including mammalian exocrine breast milk, saliva, tears and mucosal secretions (82). Lf is also present in mucosal surfaces and specific leukocyte granules and it can be found in feces following release from fecal

leukocytes (83). Abundant antimicrobial peptides and APPs are present in airway surface liquid. Lf is a bacteriostatic protein which chelates iron from $Fe3^+$ (82). Iron is required for bacterial cell division and for the development of biofilms, which are distinct, matrix-encased communities of bacteria, and the biofilm is protects against host defense mechanisms and antibiotics (84). LF chelation of iron occurs at a higher affinity in an acidic medium (85), therefore Lf binding to iron results in the prevention of growth and proliferation of iron dependent bacteria, donating this iron to beneficial bacteria, such as lactic acid bacteria (*Lactobacillales*) serves as a barrier against colonization of pathogenic bacteria on the intestinal surface thus preventing infection (84). Lf also has several other physiological roles, including stimulation of cell growth and proliferation, differentiation, development of immune competence, antifungal, antibacterial and antiviral activities, antioxidant and anti-inflammatory activity and anti-tumor activity (82,85). Recombinant Lf (TLf) produced in the filamentous fungus, *Aspergillus awamori*, possesses the same biological activities as human lactoferrin and has been reported to lower mortality in adults with severe blood poisoning (86) and to have anti-cancer activities (87,88). TLf and human lactoferrin (hLf) have been reported to display changes in immunogenicity and allergenicity in mice (89). Alteration of Lf glycosylation in human milk collected at different time points during lactation resulted in changes in bacterial binding to epithelial cells (89). Thus, hLf from milk and TLf may display different bioactivities. hLF is resistant to gastrointestinal tract digestion and may therefore play an important role in intestinal development during the prenatal period and infancy (90,91). More importantly, Lf promotes maturation of dendritic cells and therefore may function as a natural defense in neonates against bacterial invasion (90) as neonates primarily rely on innate immunity (92).

Albumin. Human serum albumin (HSA) is a major plasma protein synthesized by the liver functioning in the transport of several endogenous ligands, including fatty acids, ions, thyroxine, bilirubin; and exogenous ligands as well as drugs, such as warfarin, diazepam, phenytoin, non-estradiol anti-inflammatory drugs and digoxin (93). Albumin is a member of the family of α-fetoprotein, afamin (also called α-albumin) and vitamin D binding protein (94,95) and these proteins tend to be homologous, that is, all members of the albuminoid superfamily of proteins are suitably capable of ligand binding and transport, as they possess highly conserved intron/exon organization (95). HSA is the key regulator of fluid distribution between somatic regions of the body and body compartment (96). HSA functions to maintain plasma osmotic pressure and its synthesis is regulated by changes in blood osmotic pressure (94,97,98).

HSA is an important biomarker of inflammation in a number of diseases, including cancer, diabetes, rheumatoid arthritis, ischemia and obesity (99-101). Low expression levels of HSA may indicate malnutrition and decrease in hemoglobin levels (99). HSA serves as a valuable cell culture medium and was an additive in the production of pharmaceutical vaccines (102). HSA has also been used for decades in the management of a range of medical and surgical problems, such as for the treatment of acute hypovolemia (surgical blood loss, trauma, or hemorrhage) due to its effect on osmotic pressure

Table II. Acute phase reactants associated with vaccines.

Author, year	Vaccine	Acute phase reactant	(Refs.)
Louagie et al, 1993	Hepatitis B	Haptoglobin	(153)
Borthwick et al, 2018	Human immunodeficiency virus core DNA	Serum amyloid	(154)
Creech et al, 2017	S. aureus capsular polysaccharides	Fibrinogen	(155)
Blom et al, 1979	Typhoid. AB.-cholera	Ceruloplasmin, α-1 glycoprotein	(156)
Naylor et al, 2015	Rotavirus and poliovirus	α-1 antitrypsin	(157)
Hwang et al, 2005	Bacillus Calmette-Guerin	Lactoferrin	(158)
Carty et al, 2006	Influenza	C-reactive protein, transthyretin	(159)
Patel and Shah, 2015	H1N1 influenza	Albumin	(160)
Bos et al, 2016	Neisseria gonorrhoeae	Transferrin	(161)

providing an oncotic gradient favoring the entry of water from the interstitial space and thus reversing the movement of leaked fluids back into blood vessels (103,104).

Transferrin (Tf). Tf is a member of the iron-binding glycoprotein family, including lactoferrin (present in intracellular compartments and secretions, such as milk), melanotransferrin (present on melanoma cells) and ovotransferrin (present in egg white of multiple species), and the metal and coordinating anion sites are well conserved in all vertebrates (93). Each of these iron-binding glycoproteins features a single iron-binding site and are monomeric proteins 76-81 kDa in weight. Tf consists of two structurally similar lobes, namely, the C- and the N-lobes. Plasma transferrin provides body tissues with iron, whereas the remaining transferrin are produced locally and transport iron to restricted regions, including the testes and brain, as these two sites are relatively inaccessible to proteins in the general circulation due to the presence of highly specialized barriers (104). Liver hepatocytes are the primary sites of Tf production; however, Tf is also synthesized in other organs to a lesser extent, including the choroid plexus (105). The primary function of Tf is to transport iron from absorption centers in the duodenum and in white blood cell macrophages to all tissues (105). Tf also functions as a constituent of the innate immune system where its levels decrease during inflammation. The Tf receptor is a receptor for the IgA1 class of antibodies (106). Tf serves an important role in the somatic regions where erythropoiesis and active cell division occur (106). Iron-bound Tf is internalized by cells expressing specific Tf receptors by receptor-mediated endocytosis thus contributing to an environment with low free iron capable of inhibiting bacterial growth and multiplication during infection (96).

Transthyretin (TTR). TTR (previously referred to as prealbumin) is a negative APR synthesized and excreted by the kidneys and gastrointestinal tract with a half-life of 1.9 days and expression levels of TTR decrease significantly during inflammation which promotes an APR (96,107). TTR is also synthesized in the choroid plexus and forms a complex molecule with retinol binding protein allowing retinol and thyroxine transport (107). This process is mediated by pro-inflammatory cytokines, such as IL-6, IL-1a and TNFα (108). It has been reported that TTR functions as a biomarker for predicting poor short-term outcome and disease severity in patients with burn injuries (109,110) or respiratory failure (111), and was strongly correlated with the score of sequential organ failure assessment, and low levels of TTR were associated with an increase in mortality (112,113). Patients with low preoperative TTR levels (<0.2 g/l) are prone to increased risk of postoperative infections and need longer mechanical ventilation after heart surgery (113).

4. Vaccines and APP

Upon vaccination and introduction of antigens into the body, macrophages and dendritic cells are stimulated, producing inflammatory cytokines and triggering APP synthesis in hepatocytes, which function nonspecifically as part of the innate immune system detecting pathogens or vaccination components (114). Vaccines have been shown to cause inflammatory responses which has a direct impact on the maintenance of homeostasis, particularly in the kidney and the liver (115). Disruption of homeostasis during APR can negatively affect the host (3,7,16), for example, plasma levels of a number of microminerals, including iron, may change as they are taken up by hepatocytes and other cell types (7). As the APR increases the products of metabolism will also increase (4). The increase in the plasma proteins during APR affects the concentration of the free form of any drug administered at the time of stress, leading to drug dispersal, and variations in plasma protein concentrations during the acute phase response may result in the plasma levels of available drugs to decrease considerably whereas the total drug concentration (free and bound) will be only slightly affected, and thus the effective dose will be altered due to fluctuations in serum protein levels and decreased serum albumin expression levels (116,117). Individual variation in the expression levels of APRs in response to inflammatory stimuli, such as vaccines, has been previously reported in cattle (118), mice (119) and humans (120). This difference may be due to individual differences in inflammatory genes (120,121). Obesity can alter vaccination responses in mice, wherein the obesity was associated with decreased antibody production and ultimately reduced the efficacy of an influenza vaccine (122). Furthermore, decreased influenza-specific antibody levels and B-cell function in response to vaccination has also been linked to obesity in humans (123). Administration of vaccines containing foreign particles into the body triggers

local inflammation due to an immediate change in cytokine production, which triggers the clinical symptoms associated with vaccination. Overall, a reduced response to vaccination is a likely indication of an unregulated inflammatory system which may lead to increased risk of disease as the majority of vaccines protect against infection through induction of a B-cell antibody response (124).

Pro-inflammatory cytokine IL-6 is an important regulator of inflammation and is one of the primary cytokines which stimulate APP synthesis in hepatocytes (125-127). IL-6 functions in several processes during inflammation, including chemokine production, development of B-cells and dendritic cells, secretion and maturation of antibodies, T-cell maturation, as well as linking the innate and adaptive immune responses (128,129). An acute spike of anti-IL-6 was observed 5 days post vaccination in a small study of yellow fever vaccine, indicating its potential role predict vaccine-induced protection (130). Kurtz *et al* (131) studied the protective mechanisms of IL-6 against a *Francisella tularensis* live vaccine administered intradermally or intranasally to IL-6 knockout (KO) and wild type mice. The group reported a decline in SSA and Hp in IL-6 KO mice compared with wild type controls, indicating the importance of IL-6 in protection against infection.

In humans, the efficacy of the influenza vaccination has been invaluable. In one study, CRP expression levels increased by 36%, further increasing to 40% above baseline at day 3, before returning to the normal levels by day 7 following vaccination (132). In a study of patients >65 years old, CRP plasma concentrations spiked at 2 days post vaccination with influenza and pneumococcal vaccines as well as a combination of the two (133). Another study investigating the influenza vaccine showed that CRP expression levels post-vaccination were dependent on the dose of vaccine (134). Table II show acute phase reactants associated with vaccines.

5. Effect of adjuvant systems on APP

Adjuvants are compounds joined with other constituents in vaccine formulations (135) where multiple immunostimulants are combined with adjuvant systems to enhance antibody production and adaptive immune responses to vaccination (136). Adjuvant components regulate and improve the specificity of the immune system, thus aiming to optimize the immune response to vaccination (136). To date, there have been at least six novel adjuvants approved for use as vaccine components in the last 20 years (135,136). Adjuvant systems can be useful when strong T cell responses are required to protect against complex pathogens formed of several different types of antigens, chronic infections, or in immunocompromised populations such as the elderly or neonates (137,138). A previous study on the effects of adjuvants in rabbits indicated that CRP and fibrinogen expression levels were increased following the administration of adjuvant systems AS01, AS03, AS15 and DTPw (139). The increase in CRP levels increased 9-26-fold after injection of AS01, AS03, or AS15. Comparable effects have also been shown in humans (140). However, the use of other adjuvants such as aluminum phosphate and aluminum hydroxide did not affect CRP expression levels in the elderly or in the young following a diphtheria-tetanus-poliomyelitis-typhoid vaccine (141), influenza vaccine (142) or yellow fever vaccine (120,130). Overall, these studies indicate the efficacy of these adjuvant systems in stimulating the adaptive immune response.

6. Conclusion

APRs a group of 11 key proteins, eight of which are positive and three are negative proteins. During infection, the liver hepatocytes respond by producing a large number of APRs. Upon vaccination, an acute-phase protein reaction may develop which is a part of the innate immune system. Vaccination has also been demonstrated to cause an inflammatory response, which results in homeostatic changes including changes in renal and liver functions. Changes in APR expression levels in response to an inflammatory stimulus may vary across individuals due to genetic, nutritional, age, or other health-associated factors. The health and nutritional status of the individual may affect the response to a given vaccine due to the inflammatory condition. For example, IL-6 (an inflammatory key mediator and regulator of the majority of APRs) functions in the acute-phase protein response in the innate and adaptive branches of the immune system. CRP, as a prototypical APP, is synthesized in response to pro-inflammatory cytokine signals and CRP expression levels increase in innate immune responses to infection or to injury. Further investigations into the relationships between vaccination and the effect on CRP and other APRs may help clarify the mechanisms by which beneficial and harmful inflammatory responses affect health and influence the immune response.

Authors' contributions

RHK and NAH wrote the manuscript, edited and critically reviewed the manuscript. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

This article reflects the views of the authors and should not be construed to represent the FDA's views or policies.

Dr Humadi's contributions are an informal communication and represent his own best judgement. These comments do not bind or obligate FDA.

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