**Vaccination: Potential Adverse Effects and Future Challenges**

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**Abstract**

Concerns over potential adverse effects of vaccination have been raised with the aim to develop and design efficient yet harmless vaccines. Using data derived from the reported vaccine efficiency trials and related research, we have analyzed the possible changes in homeostasis of the hematopoietic system in terms of level of antibody (Ab) after vaccination. Several vaccines were reported to increase a wide range of total Ab concentration such as $<0.01\%-2.40\%$ in children and $0.02\%-1.65\%$ in adults. Reported increased level of IgG against *Haemophilus influenzae* type-B was recorded as 605-1210 folds higher in children and 1226-2453 folds higher in adults than the required protective levels. Similar changes were also observed for other vaccines. Such increased level of total Abs at least theoretically can contribute to higher concentration of protein i.e., hyperproteinemia in blood. Since Ab is a polymer of amino acids; therefore hyperproteinemia due to increased level of Ab may in turn affect pH and osmosis of the blood. Therefore, an optimum dose of vaccine(s) for sufficient boost of immune mechanisms, rather than a dose required for highest efficiency, is recommended before an individual is vaccinated.

**Keywords**: antibody, immunity, infection

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**Introduction**

Vaccine is a preparation of a weakened or killed pathogen, such as a bacterium or virus, or of a structural and genetic component of the pathogen that upon administration stimulates production of antibody (Ab) or cellular immunity to protect the host against the infection. New subsets of plasma
cell are usually generated to produce the Ab and other subsets of B and T-lymphocytes are generated to ensure cellular immunity (Plotkin 2003). Vaccination has been a reliable approach to eradicate infectious diseases such as diphtheria, polio and small pox (Plotkin 2003; Parslow et al. 2003; Salmon et al. 2006; Kimman and Boot 2006; de Quadros 2006; Vitek 2006). Many countries have adopted national vaccination programmes to control infectious diseases (Figure 1). Vaccination against specific infectious diseases is sometimes mandatory depending on the requirement or policy of a nation. For example measles, mumps and rubella (MMR) vaccination for healthcare workers and hepatitis A vaccination for food handlers are also required for certain nations [Immunisation Schedules. http://www.cdc.gov/vaccines/recs/schedules/default.htm#adult; Retrieved on 14th April 2010]. Similarly, meningococcal vaccination has been made mandatory while travelling to Mekkah during pilgrimage, (Saudi Ministry of Health Requirements. http://www.hajinformation.com/main/p3001.htm; Retrieved on 14th April 2010).

The haematological changes upon vaccine administration include the increased production of Ab by new subsets of plasma cells. The post-vaccination increased production of Ab may result in increased concentration of total or specific Ab in the blood. Hence the likely changes in other related haematopoietic parameters such as blood pH, osmosis may cause alteration of haematopoietic homeostasis.

Potential adverse effects of these post-vaccination changes have not been studied extensively so far. With the aid of mathematical models, a recent study (Johnson et al. 2011) described that T cell-based vaccines have the potential to generate immunopathology against viral infections. Using published data on the vaccine efficiency trials and related research, this paper demonstrates the possible post-vaccination impact on haematopoietic homeostasis. As discussed in this paper, careful attention is necessary both by the scientific community and the health care policy makers to address future challenges in vaccination programs having least or no such potential adverse effects.

Materials and methods

Data collection: Data was collected from published research articles (Table 1) based on vaccine efficiency trials, cross-sectional and cohort studies that have reported the effects of vaccination. Pre- and post-vaccination concentrations of IgG and total antibody (AbT) reported in each study were used for analyses. For comparative analysis, all reported concentrations were converted into µg/mL or percentage (%). Post-vaccination increase of IgG and AbT concentration were calculated based on either the reported pre-vaccination concentration or the average base concentration of AbT and IgG in human serum as 10mg/mL and 8mg/mL respectively (Kindt et al. 2006).

Data presented in Table 1 also include the target pathogen and the age groups. Reported ages of the subjects under each study were categorized as either children (6 weeks-14 years), adult (16-88 years), or intermediate group (3-35 years). Categorization based on age was made based on the reported age groups by the respective study. Intermediate group was categorized with individuals both from children and adult as was used by the respective study.
Figure 1: Immunisation schedules for various countries. Bar represents the time span (age) for the vaccine to be given.

Note. MY = Malaysia; UK = United Kingdom; AUS = Australia; GER = Germany; USA = United States of America; Hep B = hepatitis B; DTP = diphtheria, tetanus, pertussis; Hib = haemophilus influenza type b; OPV, IPV = polio; MMR = measles, mumps, rubella; PCV = pneumococcal conjugate.


Results

Post-vaccination changes in AbT and IgG in different age groups: The post-vaccination increase in AbT concentration were recorded in the range of <0.01%-2.40% among the children and 0.02%-1.65% among the adults. The similar changes in IgG concentration were recorded in the range of <0.01%-2.27% among the children, and <0.01%-4.6% among the adults. The intermediate
group experienced 0.22%-1.14% increase of post-vaccination IgG concentration (Table 1).

**Post-vaccination changes in Ab and IgG against different vaccines:** The post-vaccination increase in IgG and AbT against Hib vaccines have been reported in the ranges of <0.01%-2.27% and <0.01%-2.40% respectively. Similar changes in IgG and AbT concentrations against meningococcal vaccines have been found in the ranges of 0.02%-1.14% and <0.01%-1.65% respectively. Against the streptococcal vaccines, the IgG and AbT concentrations have been increased in the range <0.01-4.6% and 0.01%-0.35% respectively (Table 1).

**Discussion**

**Post-vaccination level of Ab may reach far more than the required protective levels:** The accepted protective level (concentration) of Ab is specific to type and dose of the infectious agent. For example, the minimum geometric mean concentration (GMC) of Ab against Hib for short term protection is ≥0.15 µg/mL, while that for long term protection is ≥1.00 µg/mL (Southern et al. 2009). Protective Ab concentrations against meningococcal group C infections are accepted to be ≥0.3µg/mL (Schmitt et al. 2007), while that against pneumococcal infection is >0.2µg/mL (Navarro et al. 2006). However, as presented in the Table 1, the IgG and AbT concentration against Hib vaccine in children can reach as high as 181.6 µg/mL, and 240.0 µg/mL respectively. Similar vaccines given to adults may result in 368.0 µg/mL for IgG and 163.0 µg/mL for AbT (Table 1). As compared to the minimum protective level, these level (concentration) of vaccine-induced Abs is far more than the required minimum GMC. Similar observations on excessive amount of vaccine-induced Ab can be drawn for other vaccines.

Post-vaccination amount of AbT or IgG against a specific vaccine may vary depending on individuals’ age (Southern et al. 2007), nutritional status (Moriguti et al. 2005) and environmental factors (Gajdusek and Brown 1970). Nonetheless, those recorded values of changes in Ab concentration are indeed much higher than the required minimum GMC. For example, the level of IgG against Hib in children and adults may be 605-1210 and 1226-2453 fold higher than the required protective levels respectively. Similar magnitude of increased levels of Abs compared to the respective protective levels can be observed against other pathogens. For example, the levels of Ab against Hib, meningococcal and streptococcal vaccines are about 1210, 304 and 1840 fold higher respectively than the minimum protective levels.

**Potential impact: hyperproteinemia due to excessive post-vaccination Ab levels:** The calculations given above on the excessively increased levels of post-vaccination Ab may contribute to the increased concentrations of proteins in the blood. Hence, the cumulative amount of post-vaccination Abs due to multiple vaccines given to one individual is expected to result in hyperproteinemia. In other words, the practice of administering multiple vaccines, a regular practice as childhood vaccination program (Figure 1), can contribute to an increased concentration of post-vaccination Abs resulting in hyperproteinemia in circulation. Notably, average protein concentration in blood is approximately 5.5-8.0g/dL with IgG making up about 80% of total serum immunoglobulin (Kindt et al. 2006; Gerbino 2005). Therefore excessive amount of IgG alone can contribute to the postulated hyperproteinemia.

This notion can also be supported by the observation that administration of tetanus toxoid vaccine increased antibody concentrations as high as 162-fold compared to the pre-vaccination values, while antibody concentrations specific to other unrelated antigens remained constant over the period of follow-up (Di Genova et al. 2006). In other words, each unrelated vaccine would contribute to hyperproteinemia due to increased Ab concentration independently.

Biochemically Abs like other proteins are polymers of amino acids. Because of the chemical composition and ionic states of the Ab, hyperproteininaemia due to its increased amount, eventually could affect pH, osmolality and the serum osmolar gap (Steinberger et al. 2003). Blood pH in the narrow range of 7.35-7.45 is required to ensure proper metabolic processes and transport of both oxygen and carbon dioxide. While certain pathological conditions interfering pH controlling mechanisms alters physiological pH range, changes in pH beyond physiological range can also cause pathological conditions. For example, acidosis (pH lower than the physiological range) or acute acidosis may be associated with fatigue, nausea, and vomiting, an increased rate and depth of breathing, confusion, and headaches, seizures, coma, and in some cases death. Similarly alkalosis (pH above 7.45) is associated with irritability, weakness, and cramping.
Table 1: Description of research articles used as source of data

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pathogen</th>
<th>Age group</th>
<th>N</th>
<th>% Changes in Ab concentration</th>
<th>IgG</th>
<th>AbT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baggett et al., 2006</td>
<td>Hib</td>
<td>I</td>
<td>47</td>
<td>0.22-0.24</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Baker, 1978</td>
<td>StrepA</td>
<td>A</td>
<td>22</td>
<td>N/A</td>
<td>0.02-0.11</td>
<td></td>
</tr>
<tr>
<td>Barington et al., 1991</td>
<td>Hib</td>
<td>A</td>
<td>43</td>
<td>N/A</td>
<td>0.15-0.34</td>
<td></td>
</tr>
<tr>
<td>Barington et al., 1994</td>
<td>Hib</td>
<td>C</td>
<td>144</td>
<td>N/A</td>
<td>0.07-0.11</td>
<td></td>
</tr>
<tr>
<td>Beuvery et al., 1982</td>
<td>MenA, MenC</td>
<td>A</td>
<td>66</td>
<td>0.02</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Borrow et al., 2003</td>
<td>MenC</td>
<td>C</td>
<td>540</td>
<td>0.10-0.36</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2007</td>
<td>MenC</td>
<td>C</td>
<td>540</td>
<td>0.10-0.36</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Beuvery et al., 1982</td>
<td>MenA, MenC</td>
<td>A</td>
<td>66</td>
<td>0.02</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Baker, 1978</td>
<td>StrepA</td>
<td>A</td>
<td>22</td>
<td>N/A</td>
<td>0.02-0.11</td>
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<tr>
<td>Barington et al., 1991</td>
<td>Hib</td>
<td>A</td>
<td>43</td>
<td>N/A</td>
<td>0.15-0.34</td>
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<tr>
<td>Barington et al., 1994</td>
<td>Hib</td>
<td>C</td>
<td>144</td>
<td>N/A</td>
<td>0.07-0.11</td>
<td></td>
</tr>
<tr>
<td>Beuvery et al., 1982</td>
<td>MenA, MenC</td>
<td>A</td>
<td>66</td>
<td>0.02</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Borrow et al., 2003</td>
<td>MenC</td>
<td>C</td>
<td>540</td>
<td>0.10-0.36</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2007</td>
<td>MenC</td>
<td>C</td>
<td>540</td>
<td>0.10-0.36</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Cryz et al., 1987</td>
<td>PseuA</td>
<td>A</td>
<td>N/A</td>
<td>&lt;0.01-2.2</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Dagan et al., 1998</td>
<td>Hib</td>
<td>C</td>
<td>75</td>
<td>N/A</td>
<td>0.03-0.20</td>
<td></td>
</tr>
<tr>
<td>Denel et al., 2007</td>
<td>Hib</td>
<td>C</td>
<td>170</td>
<td>0.03-0.54(US)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Gold et al., 1975</td>
<td>MenA</td>
<td>C</td>
<td>396</td>
<td>&lt;0.01-0.04</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Gotschlich et al., 1972</td>
<td>MenC, MenA</td>
<td>C</td>
<td>167</td>
<td>0.09-0.39</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Guimaraes et al., 2002</td>
<td>Hib</td>
<td>C</td>
<td>111</td>
<td>0.34</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Jelonek et al., 1993</td>
<td>Hib</td>
<td>C</td>
<td>107</td>
<td>&lt;0.01-0.15</td>
<td>&lt;0.01-2.40</td>
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</tr>
<tr>
<td>Jokhdar et al., 2003</td>
<td>MenA, MenC</td>
<td>I</td>
<td>230</td>
<td>0.34-1.14</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Kasper et al., 1996</td>
<td>StrepA</td>
<td>A</td>
<td>90</td>
<td>&lt;0.01-4.6</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Kroon et al., 1999</td>
<td>Tet</td>
<td>A</td>
<td>29</td>
<td>0.03-1.03</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Lee et al., 2009</td>
<td>StrepP</td>
<td>C</td>
<td>31</td>
<td>0.04-0.13</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Navarro et al., 2006</td>
<td>StrepP</td>
<td>C</td>
<td>14</td>
<td>0.13-0.50</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Puumalainen et al., 2003</td>
<td>StrepP</td>
<td>C</td>
<td>92</td>
<td>N/A</td>
<td>0.01-0.33</td>
<td></td>
</tr>
<tr>
<td>Richmond et al., 1999</td>
<td>MenC</td>
<td>C</td>
<td>115</td>
<td>N/A</td>
<td>0.10-0.19</td>
<td></td>
</tr>
<tr>
<td>Rose et al., 2005</td>
<td>StrepP</td>
<td>C</td>
<td>33</td>
<td>&lt;0.01-0.16</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Rubins et al., 1999</td>
<td>StrepP</td>
<td>A</td>
<td>53</td>
<td>0.04-0.25</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Schmitt et al., 2007</td>
<td>MenC, HiB</td>
<td>C</td>
<td>520</td>
<td>0.03-0.35</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Southern et al., 2004</td>
<td>MenC</td>
<td>A</td>
<td>103</td>
<td>0.49-0.56</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Southern et al., 2007</td>
<td>Hib</td>
<td>C</td>
<td>388</td>
<td>0.37-2.27</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Southern et al., 2009</td>
<td>Hib</td>
<td>C</td>
<td>367</td>
<td>0.02-0.05</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Vu DM et al., 2006</td>
<td>MenC</td>
<td>A</td>
<td>61</td>
<td>0.05-0.09</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Wuorimaa et al., 2001</td>
<td>StrepP</td>
<td>C</td>
<td>251</td>
<td>&lt;0.01-0.23</td>
<td>N/A</td>
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<tr>
<td>Zollinger et al., 1978</td>
<td>MenB</td>
<td>A</td>
<td>8</td>
<td>N/A</td>
<td>0.17-1.65</td>
<td></td>
</tr>
</tbody>
</table>

Note. N/A = not available; C = Children; A = Adults; I = Intermediate; Hib = Haemophilus influenzae type B; StrepA = Streptococcus agalactiae; MenA = meningococcal group A; MenB = meningococcal group B; MenC = meningococcal group C; StrepP = Streptococcus pneumoniae; PseuA = Pseudomonas aeruginosa

a Age range was not given for these studies, but results were reported to be from adult subjects

b Separate studies conducted in USA and in Germany

It might be argued that excessive amount of post-vaccination Ab is observed only in few cases as reported. For example, in the study evaluating the effect of vaccination on specific and bystander antibody responses, the most dramatic changes were observed in 2 out of 12 subjects (Di Genova et al. 2006). This smaller ratio however may represent a large number of individuals since vaccination program often includes a mass population.

It has been reported earlier (Vauloup-Fellous and Grangeot-Keros 2007) that responses towards natural antibody and vaccination are not the same. IgM and IgG responses were dissimilar
between individuals who are vaccinated and naturally exposed to Rubella virus. Individuals exposed to Rubella naturally tend to have higher post-exposure antibody levels compared to that of individuals exposed to vaccine but the rate of its decline is rapid. The level of post-exposure IgG after natural infection remains for about 2 months, whereas post-vaccination IgG remained for about 5 months. This adds further concern of hyperproteinemia due to vaccination for a prolonged period of time.

The challenge: optimum type and dose of vaccine(s) at individual level

The discussion above might suffice to raise the concern of finding an optimum dose of vaccine for an individual to induce the protective level of Ab at individual level while not being excessive leading to potential pathological consequences. In other word, vaccination program should be carefully carried out to ensure that potentials harms do not outweigh the benefits. Notably, in 1972 the USA ceased vaccination against smallpox because the risks were judged to outweigh the benefits (Lane and Goldstein 2003). To find an optimum dose and number of vaccination, the following observations should be given proper attention.

Strength of an individual's natural immune system: Every healthy individual is born with all necessary innate and adaptive immune mechanisms that evolve in time with every exposure of foreign particle. Natural immune mechanisms are highly efficient both in recognition and fighting pathogens or infectious agents. For example, 14 out of 24 chronic hepatitis patients reportedly cleared all HbeAg after a 6-year period of follow up of which 10 individuals eventually developed anti-Hbe naturally (Sakugawa et al. 1991). Although, depending on the dose and type of the pathogens, the consequence of the infection varies from recovery i.e., complete removal of the pathogens to diseased condition which in turn may result into death, the above example explains that a large number of individuals have the ability to activate natural immune mechanisms to prevent the infectious consequences. Therefore, strength of the natural immune mechanisms of an individual should be considered before s/he is brought under random vaccination.

Immune responses to natural infection differ from vaccination: It is also important to consider that immune response against natural infection generates higher Ab titer compared to immune response against vaccination. Again, decay of Ab generated due to natural infection is faster than that generated due to vaccination (Vauloup-Fellous and Grangeot-Keros 2007). Such difference in Ab titer and their subsequent decay may raise the concern of proper dose of vaccination which would generate more natural course of immune response.

Maternal antibodies can reduce the risk of infection in infants: It has been reported that maternal antibodies passed down to infant via the placenta, or by breastfeeding can confer immunity, at least against some diseases, such as septicemia, otitis media, celiac disease, and other diseases (Newman 1995). Furthermore, in a prospective study (Sadéharjú et al. 2007) where infants were followed up from birth and were monitored for enterovirus infections, it was observed that duration of breastfeeding and levels of enterovirus-specific antibodies in breast milk and blood samples are correlated. Infants exclusively breastfed for more than two weeks had fewer enterovirus infections by the age of one year compared with those exclusively breastfed for less than two weeks. High maternal Ab levels in serum and in breast milk were associated with a reduced frequency of infections. This effect was seen only in those infants breastfed for more than two weeks, indicating that breast milk antibodies mediate this effect. Breast feeding for appropriate duration therefore may reduce the requirement of mass vaccination.

Research on long-term impact of vaccination is required: All over the world infants/children are subject to extensive vaccination programmes (Figure 1). Lack of study on the long-term effects of such vaccination limits the understanding of any lasting impact, if there is any, on their health in adulthood. Besides safety concern on short term pre-clinical trials is not new. For example, the drug Vioxx was withdrawn from the US market in 2004 amid a meta-analysis proving an increased relative risk of myocardial infarctions associated with the use of the drug, while pre-clinical trials found that drug safe for consumption (Horton 2004). Hence, long-term impact of vaccination should be studied carefully to prevent anything similar from happening.

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