Queensland
Allergy Services

21 October 2013

Re: **Proposal 274**

Submissions on proposal to amend minimum age labeling on infant foods

I STRONGLY REJECT the proposal to change to “around 6 months”. This is a woolly and non-evidence based change in the current recommendation of 4-6 months.

Non-evidence based recommendations of avoiding certain solids in the late 90’s has been associated with a **surge in severe food allergies we have observed in the last 20 years**. The early studies on early introduction of protein load in infancy showed safety in terms of renal sufficiency but increased atopic dermatitis. From first principles, if a child is hungry and can chew and swallow, they are probably ready to eat. It does not make sense for a group of experts tell parents to wait 6 rotations of the moon around earth before letting their child eat.

A non-defined time of “around 6 months” in proposal 274 will mean consumption in the 7^{h} month onwards by a significant proportion of infants. By this time, protective passively transferred maternal antibodies will largely have disappeared.

I have summarised details relating to tolerance antibodies below:

Immunoglobulin’s A and IgG4 are associated with tolerance. It is widely recognized that maternal antibodies’ pass via the placental circulation to provide immunological protection at many levels for the newborn. The half life of IgG is generally regarded at approximately 30 days, however in the newborn, binding to the fetal IgG receptor provides a reservoir (in tissues such as the endothelium) to last for several months until the infant develops functional self-capacity[1]. It has only been recently appreciated the IgA in the newborn infant is virtually all from maternal sources as demonstrated in Guthrie card analysis of IgA replete newborns from IgA deficient mothers and the cards of children with IgA deficiency, born to IgA replete mothers[2]. At birth, secretory IgA is undetectable, but rises in the presence of microbial and food protein antigenic stimuli to adult levels at between 6 months and three years of age[3,4].

The neonatal Fc receptor (FcRn) transfers IgG from the mother across the placenta and the proximal small intestine. This helps to confer short-term passive immunity[1]. The binding and transfer of maternal IgG from apical to underlying extracellular space is very pH dependent (pH<5.4). The acidic environment of the duodenum, is optimal for binding of maternal IgG to the FcRn and after transfer to the extracellular space which is less acidic and this promotes disassociation of IgG. The absence of FcRn in a murine model demonstrated inability to absorb IgG from maternal milk[5].

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The association of food allergy with antacids[6] may involve inhibition of maternal IgG binding to the upper GI lumen. IgA is transferred via a similar mechanism, involving the polyimmunoglobulin receptor (pIgR).

It has been demonstrated that about 2% of food proteins can pass directly through to the gut sub-mucosa in a relatively intact form and is capable of activating mast cells[7]. Sub-mucosal IgA and IgG4 are likely to be important in tolerance responses to dietary antigen and their absence can contribute to food allergy. A transiently low serum IgA at 3 months of age has been associated with the development of atopy in the first year of life[8]. IgE responses to milk proteins have been correlated with physiologically low IgA and deficient conditions[9-11.] In a germ free environment, IgA deficient rabbits experienced food allergy and anaphylactic death with milk exposure[12]. IgG4 is important in competing with IgE for facilitative activation of T cells and sensitization of mast cells[13]. Tolerance to milk proteins has been correlated with IgG4 levels[14].

Absence of IgA and IgG4 may occur from lack of passive transfer, lack of production (immunological immaturity or gene defect), inhibition of FcRn by antacids, loss though increased GI permeability, or consumption (larger amounts of food or increased food permeability via mucosa). The window of tolerance (or opportunity) may be in part, explained by the relative influences on IgA and IgG4 in the first 6-7 months of life. These factors are summarized in a schema (figure 1)

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"Infant Tolerance Antibodies"

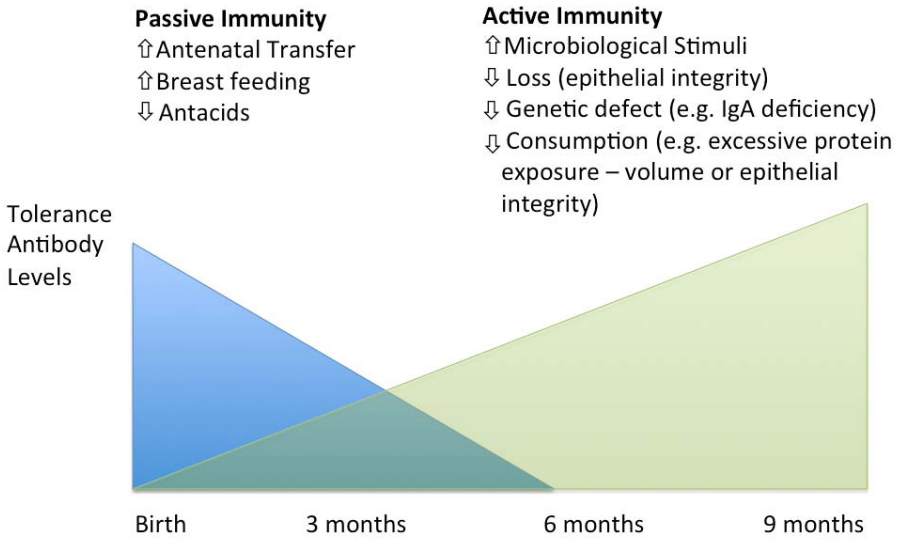

Figure 1. The window of opportunity for tolerance to food proteins may be vulnerable to lack of tolerance antibodies. Passive immunity with some IgA and IgG antibodies are transferred in the antenatal period. In the post-natal period maternal tolerance antibodies can be absorbed by the suckling newborn, however antacids can interfere with luminal binding of IgG with the FcRn. The active immune response with synthesis of IgG4 and secretory IgA is enhanced with microbiological stimuli. Tolerance antibodies may not be produced with certain gene defects, lost due to impaired epithelia integrity or consumed with increased antigen exposure, either form consumption or impaired epithelial integrity leading to greater sub-mucosal food antigen exposure.

IgE is the effector antibody in allergic responses. Maternal IgE can be passively transferred to the fetus via swallowed amniotic fluid[15]. IgE from the fetus or infant can also be secreted into the gut lumen. Within the gut, CD23 binds to IgE, in a similar manner as IgG does with the FcRn and can transport IgE bound to food proteins to sensitize mast cells, basophils and influence the function of dendritic cells and lymphocytes[16].

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3. Sahvilati E. Immunoglobulin-containing cells in the intestinal mucosa and immunoglobulins in the intestinal juice in children. Clin Exp Immunol. 1972; 11: 415–425.

4. Crabbé PA, Nash DR, Bazin H, Eyssen H, Heremans JF. Immunohistochemical observations on lymphoid tissues from conventional and germ free mice. Lab Invest. 1970;22:448-57.

5. Roopenian DC, Christianson GJ, Sproule TJ, Brown AC, Akilesh S, Jung N, Petkova S, Avanessian L, Choi EY, Shaffer DJ, Eden PA, Anderson CL. The MHC class I-like IgG receptor controls perinatal IgG transport, IgG homeostasis, and fate of IgG-Fc-coupled drugs. J Immunol. 2003 Apr 1;170(7):3528-33.

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7. Husby S, Jensenius J, Svehag S. Passage of undegraded dietary antigen into the blood of healthy adults. Quantification, estimation of size distribution and relation of uptake to levels of specific antibodies. Scand J Immunol 1985;22:83-92.

8. Taylor B, Norman AP, Orgel HA, Stokes CR, Turner MW, Soothill JF. Transient IgA deficiency and pathogenesis of infantile atopy. Lancet. 1973 Jul 21;2(7821):111-3.

9. Kletter B, Gery I, Freier S, Davies AM. Immune responses of normal infants to cow milk. I. Antibody type and kinetics of production. International Archives of Allergy and Applied Immunology. 40, 656-666

10. Buckley RH, Dees SC Correlation of milk precipitins with IgA deficiency NEJM 1969, 281:465-469.

11. Tomasi TB, Katz L . Human antibodies against bovine immunoglobulin M in IgA deficient sera. Clin Exp Immunol. 1971; 9: 3–10.

12. Coates ME. & O'Donoghue PH. Milk allergy in infant germ-free rabbits. *Nature* 213, 307-308

13. Aalberse RC, Stapel SO, Schuurman J, Rispens T.Immunoglobulin G4: an odd antibody. Clinical & Experimental Allergy, 2009; 39:469–477.

14. Ruiter B, Knol EF, Van Neerven RJ et al. Maintenance of tolerance to cow's milk in atopic individuals is characterized by high levels of specific immunoglobulin G4. Clin Exp Allergy 2007; 37:1103–10.

15. Thornton CA, Holloway JA, Popplewell EJ, Shute JK, Boughton J, Warner JO. Fetal exposure to intact immunoglobulin E occurs via the gastrointestinal tract. Clin Exp Allergy. 2003;33:306–311.

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TIMING OF INTRODUCTION OF FOODS

There are obvious children who the age of introduction of weaning food does not involve risk (the immunologically bulletproof). Early complementary feeding (<4 months has been associated with eczema, even out to 10 years). Fergusson DM, Pediatrics 1990;86:541-6 and this lead to studies (which did not show allergy risk reduction) which proposed late introduction of "at risk" solids which evolved into complex weaning guidelines adopted in several countries. The inconsistency of this data is made less credible by Ziegler having different introduction protocols for solids in the two papers from the same patient subset and over a 40% drop out from ITT as well as 5 interventions in the one study, of which timing of foods was only one component.

There is data that risk of food sensitisation and allergy is increased with later introduction. This is shown in multiple studies (e.g. Bright I. Nwaru et al. Age at the Introduction of Solid Foods During the First Year and Allergic Sensitization at Age 5 Years Pediatrics. 2010 125:50-9) and emphasized in recent reviews that delay of solids may do harm (Agostoni C,, Decsi T, Fewtrell M et al JPGN 46:99–110, 2008; Prescott SL, Smith P, Tang M, et al.. Pediatric Allergy and Immunology 2008, 19: 375-380; Greer FR, Sicherer SH, Wesley Burks AW et al. *Pediatrics* 2008;121;183-191)

The NH&MRC review Box 1.2 **misquoted** the window of tolerance as being "around 6 months". This is being carried over into proposal 274. (Prescott SL, Smith P, Tang M, et al.. Pediatric Allergy and Immunology 2008, 19: 375-380). We did discuss a window between 4-7 months.

A systematic review, commissioned in the late 1990s specifically addressed the optimal age for introducing solid foods and included studies in both breast-fed and formula-fed infants. The authors concluded that there was no compelling evidence to support a change in the 1994 UK Department of Health recommendation or the (then current) WHO recommendation (both 4 – 6 months). (Lanigan J, Bishop JA, Kimber AC, et al. Systematic review concerning the age of introduction of complementary food to the healthy full-term infant. Eur J Clin Nutr. 2001; 55: 309 – 20.)

In the prospective DAISY study, risk of wheat allergy was increased with both too early and **too late introduction of wheat**. (Poole JA et al. Pediatrics 2006, 117: 2175-82). Coeliac disease is higher in those where wheat is introduced earlier and later (and this is increased in those with a higher genetic risk. (Norris JM, Barriga K, Hoffenberg EJ et al. JAMA 2005, 293: 2343-2351). The same story goes for diabetes and early and late wheat. (Norris JM, Barriga K, Klingensmith G et al. JAMA 2003, 290: 1713-1720; Zieglier AG, Schmid S, Huber D JAMA 2003, 290: 1721-1728). Katie Allen and Sue Prescott's group have work on early egg / baked egg and allergy / sensitization risk. There is also protective data on having fish in the first year. (Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. Allergy 2006;61:1009-15.). George Du Toit's ethnographic data on peanut allergy (Levy Y, et al, Allergy 2003: 58:1206-1207; Du Toit G. J Allergy Clin Immunol 2008;122:984-91) where early exposure to peanut in a boiled peanut snack in infancy is associated with lower risk of PA in Israel.

DOSE is of food Important. With Coeliac disease and wheat, the there was a higher rate of CD in Swedish vs Danish groups despite being genetically similar. (Carlsson AK et al Pediatrics 2001, 107: 42-45). The coeliac disease prevalence in 2-3 year olds 1.03% vs 0.39% with "higher gluten ingestion feeding rules of the 80's in Sweden (Laurin P et al. Scan J Gastroenterol 2004; 39: 946-52).

Breast feeding while introducing complementary feeds appears to be beneficial

Higher levels of tolerance IgA antibodies to cows milk are observed in infants of BF mothers (Piirainen LL et al PAI 2009: 20: 295–298)

With respect to Coeliac disease the meta-analysis on BF while introducing wheat showed this was protective (Akonberg AK et al Arch Dis Child 2006, 91: 39-43). This included the 4 studies below.

Ivarsson A, et al Am J Clin Nutr 2002, 75: 91-921

Ascher H, et al Arch Dis Child 1997, 76, 113-118

Fatih-Magnusson K, et al Pediatric Allergy Immunol 1996, 7:1-5

Peters U, et al Ann Nutr Metabl 2001, 45: 135-42

In 2011, we know from that analysis of over 50 000 individuals in the ISAAC study that for severe eczema, breastfeeding *per se* conveyed a risk reduction on sleep disturbed eczema (pooled adjusted OR 0.71, 95% CI 0.53–0.96), **but this effect was lost where children had been exclusively breastfed for > 4 months** (pooled

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adjusted OR 1.02, 95% CI 0.67–1.54). (Flohr C et al British Journal Dermatology August 2011). **This is very strong evidence of likelihood of arm with proposal 274.**

The above mega-study reinforces that by Michael Kramer in the BMJ in 2007 (which was controversial at the time – they looked at over 17000 mother baby pairs and followed up allergy and asthma to 6.5 years. Kramer MS et al . BMJ 2007, 335 : 815

Results The experimental intervention led to a large increase in exclusive breast feeding at 3 months (44.3% *v* 6.4%; P<0.001) and a significantly higher prevalence of any breast feeding at all ages up to and including 12 months. The experimental group had no reduction in risks of allergic symptoms and diagnoses or positive skin prick tests. In fact, after exclusion of six sites (three experimental and three control) with suspiciously high rates of positive skin prick tests, risks were significantly increased in the experimental group for four of the five antigens.

Conclusions These results do not support a protective effect of prolonged and exclusive breast-feeding on asthma or allergy.

I am concerned that the around 6 months will lead to a large percent of children being introduced to solids in the 7 ^{h} month or later. It will also put Australia out of step with European evidence based recommendations for allergy

Thank you for your consideration of my comments.

Yours sincerely

[redacted]

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