

**Role of 100% Whey Protein  
Partially Hydrolyzed in Infant Formula  
&  
Reducing the Risk of  
Allergy in Healthy Infants**

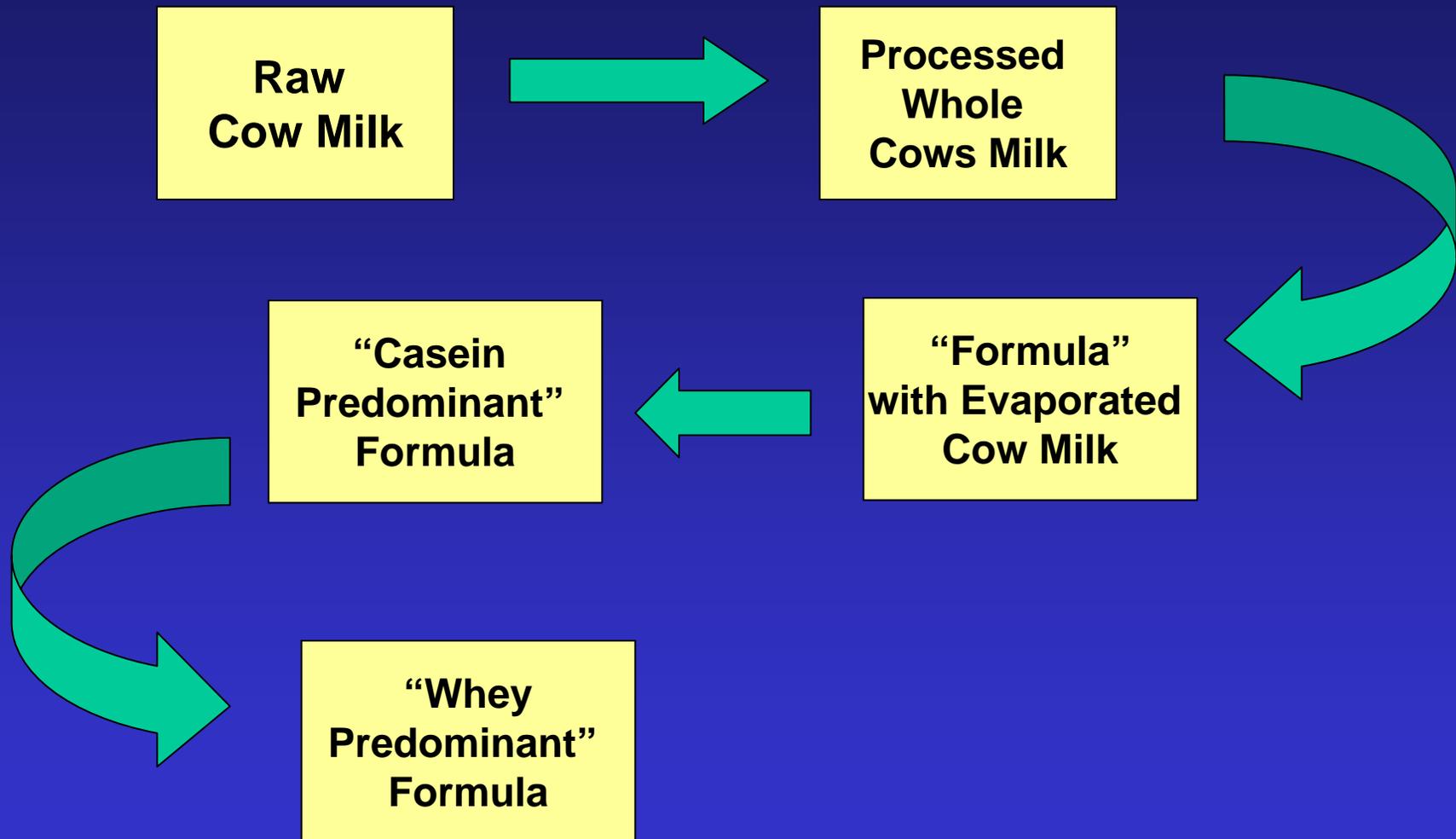
**Rationale and Substantiation  
for a Qualified Health Claim**

# The Standard

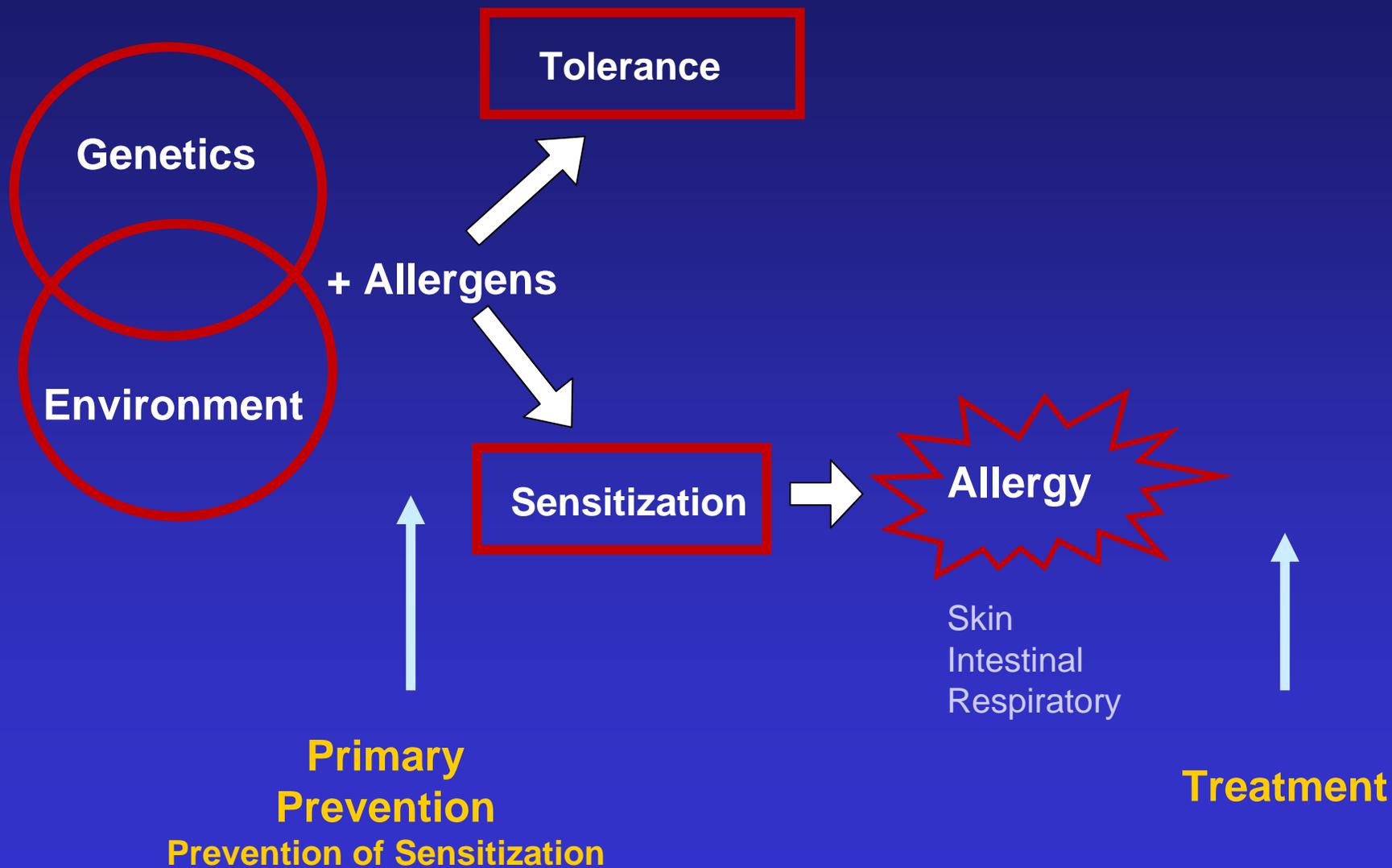


- Nutritionally
- Functionally

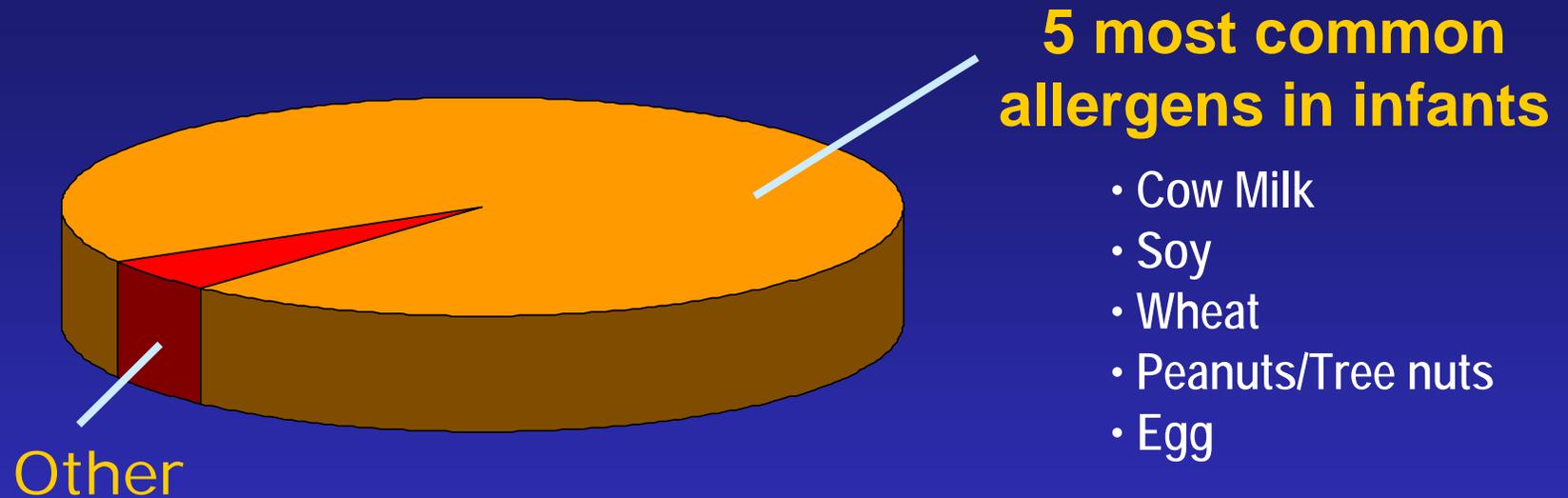
Historically, formulas have evolved to make cow's milk nutritionally and functionally closer to human milk



# Pathogenesis and Prevention of Allergic Disease



# Food Allergies: 90% accounted for by 5 foods

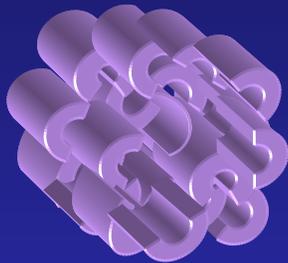


## **Cow milk protein:**

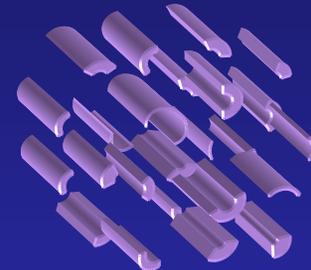
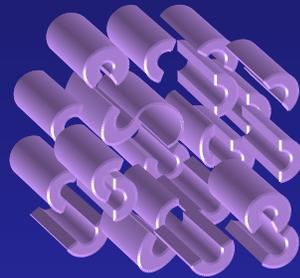
- the most common food antigen in infants
- the most common protein used in infant formulas

# Protein Size and Allergic Reactions

Intact Proteins



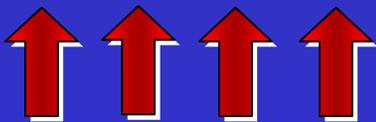
Hydrolyzed Proteins



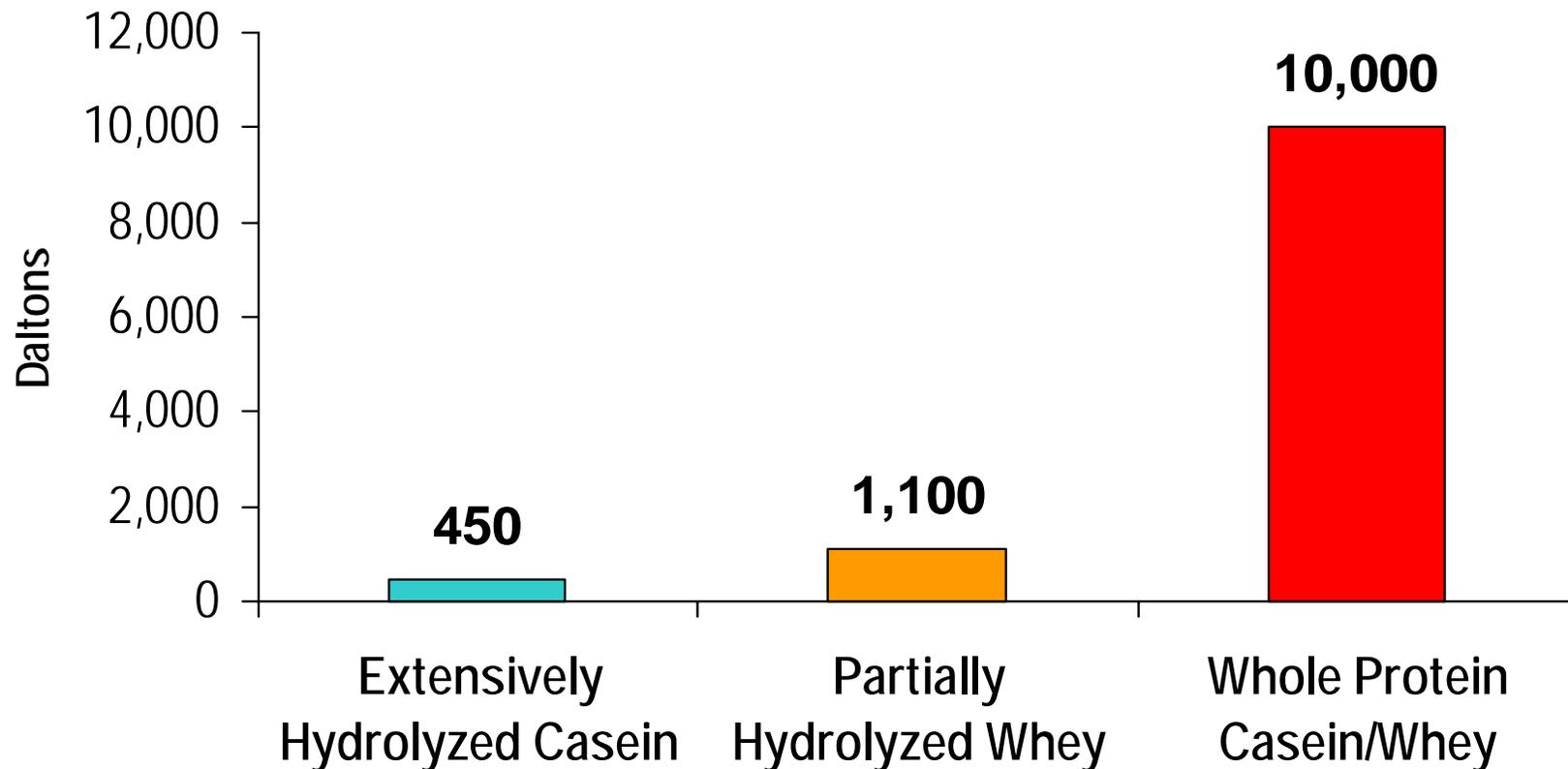
Processing by the Intestinal Immune System



Chance for Allergic Reaction



# Hydrolysis Can Reduce Allergenicity of Cow Milk Proteins



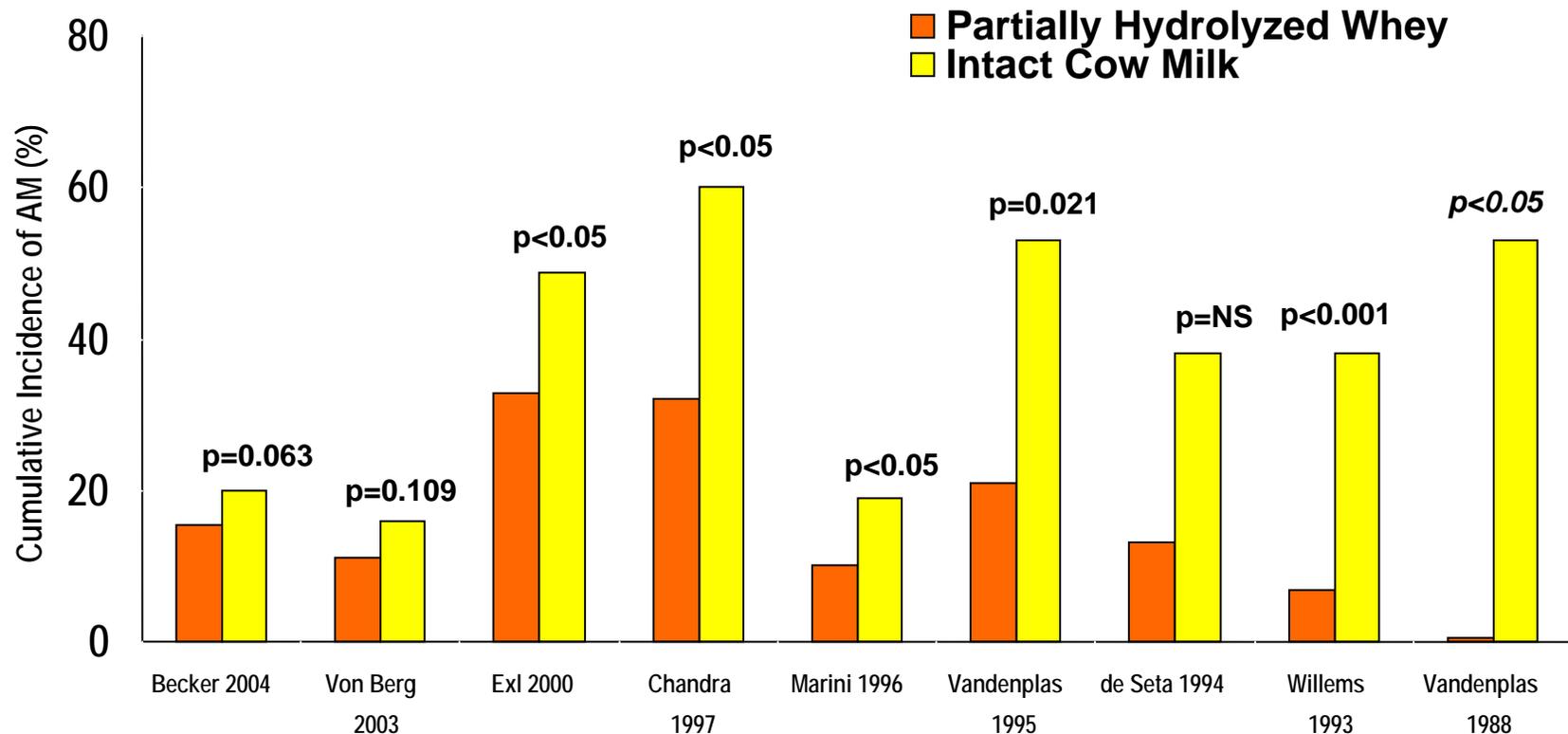
Median Molecular Weight of Infant Formulas

# 100% Whey Protein Partially Hydrolyzed To Reduce the Risk of Allergy

- Strong theoretical basis
- Controlled clinical trials
  - 18 Published clinical trial reports (various ages)
  - 12 independent patient cohorts
  - Varying size, design, significance, quality
  - Most done in infants with a family history of allergy
- All showed a reduction in incidence of atopic disease

# Cumulative Incidence of Atopic Manifestations < 12 months of age

## 100% Whey Protein Partially Hydrolyzed Formula vs Cow Milk Formula in Prevention Studies



\* Graph depicts only published, peer-reviewed, prospective trials with data collection at timepoints  $\leq 12$  months.

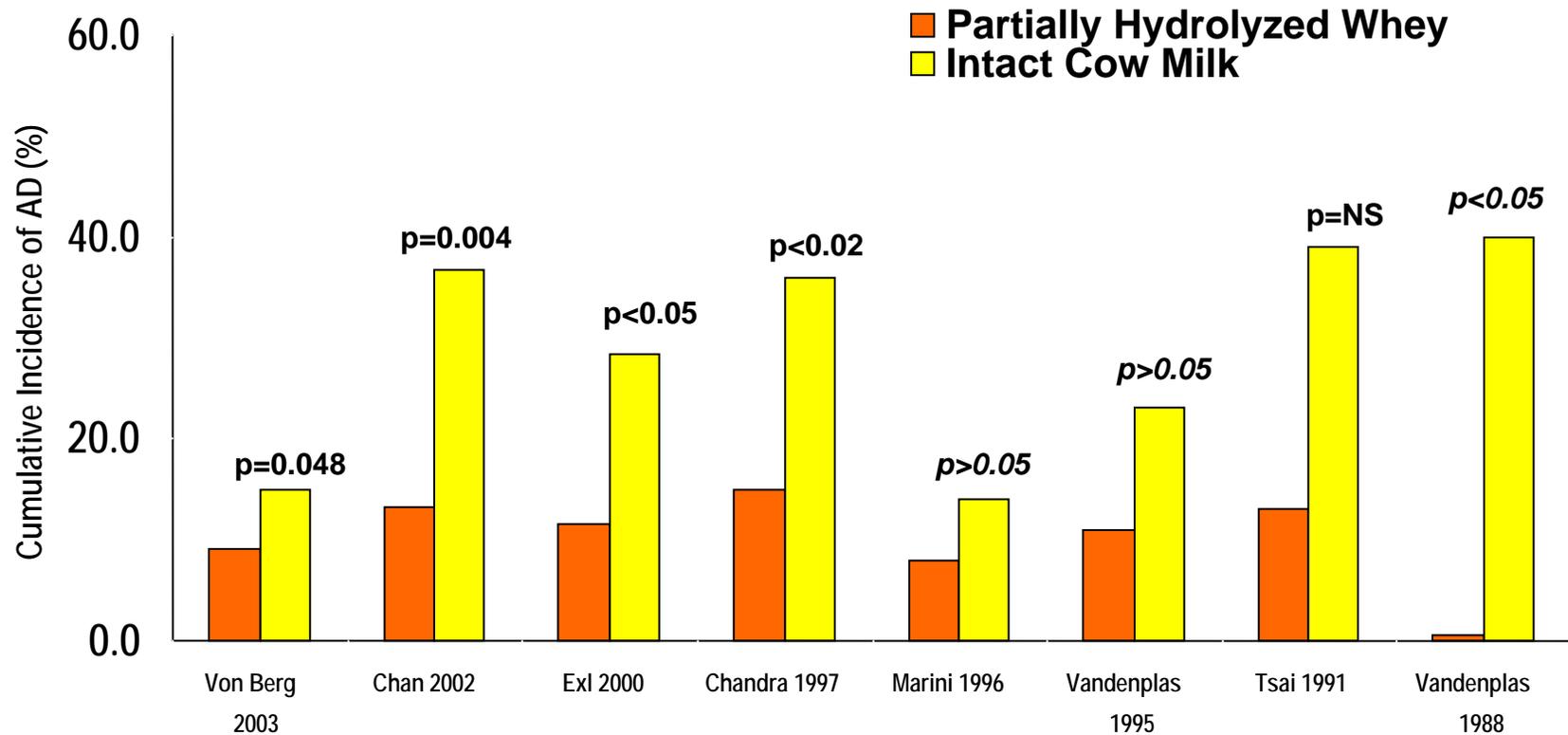
\*\* For all studies except Becker 2004, AM includes AD as one of the allergic outcomes assessed; for Becker 2004, AM refers to asthma alone.

\*\*\* 4 months: Vandenplas 1988; 6 months: Exl 2000, De Seta 1994; 12 months: Becker 2004, Von Berg 2003, Chandra 1997, Marini 1996, Vandenplas 1995, Willems 1993

\*\*\*\* p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and CI

# Cumulative Incidence of Atopic Dermatitis < 12 months of age

100% Whey Protein Partially Hydrolyzed Formula vs Cow Milk Formula in Prevention Studies



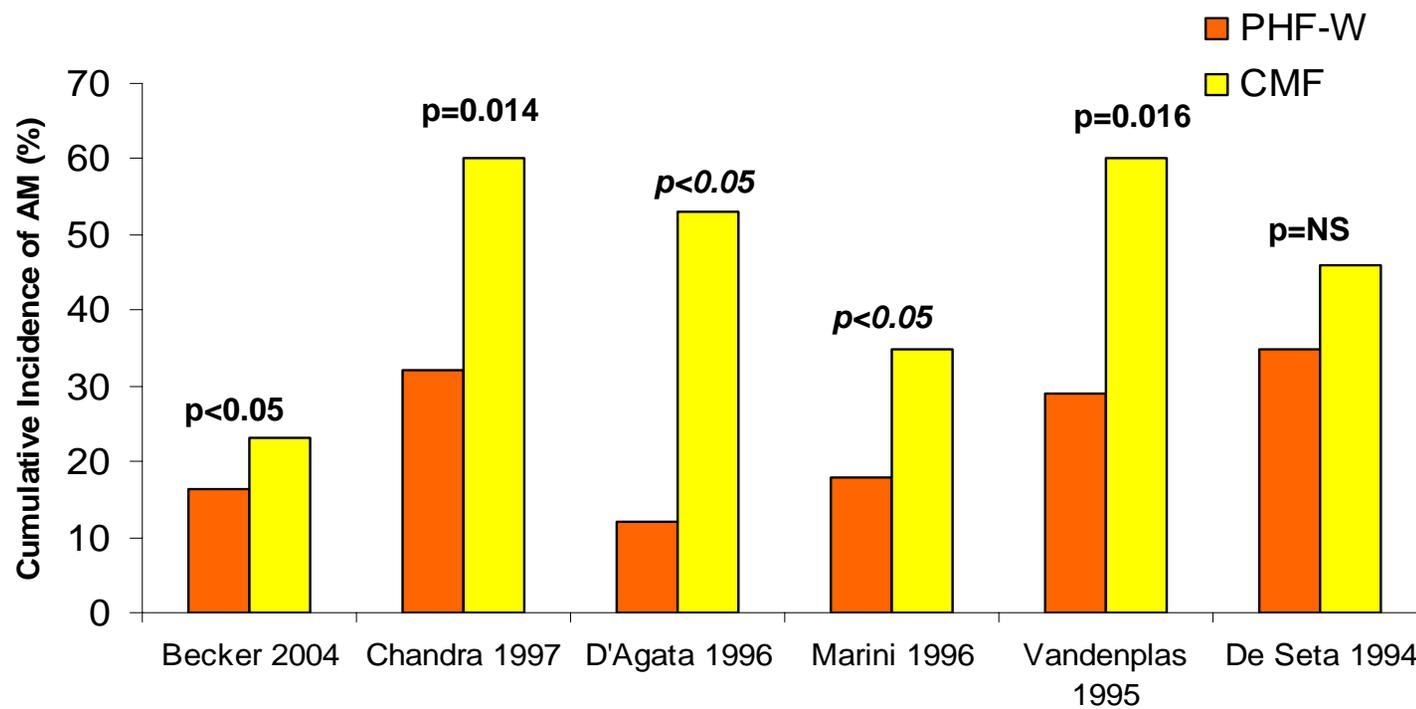
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# Cumulative Incidence of Allergic Manifestations > 12 mo of Age

100% Whey Protein Partially Hydrolyzed Formula vs Cow Milk Formula in Prevention Studies

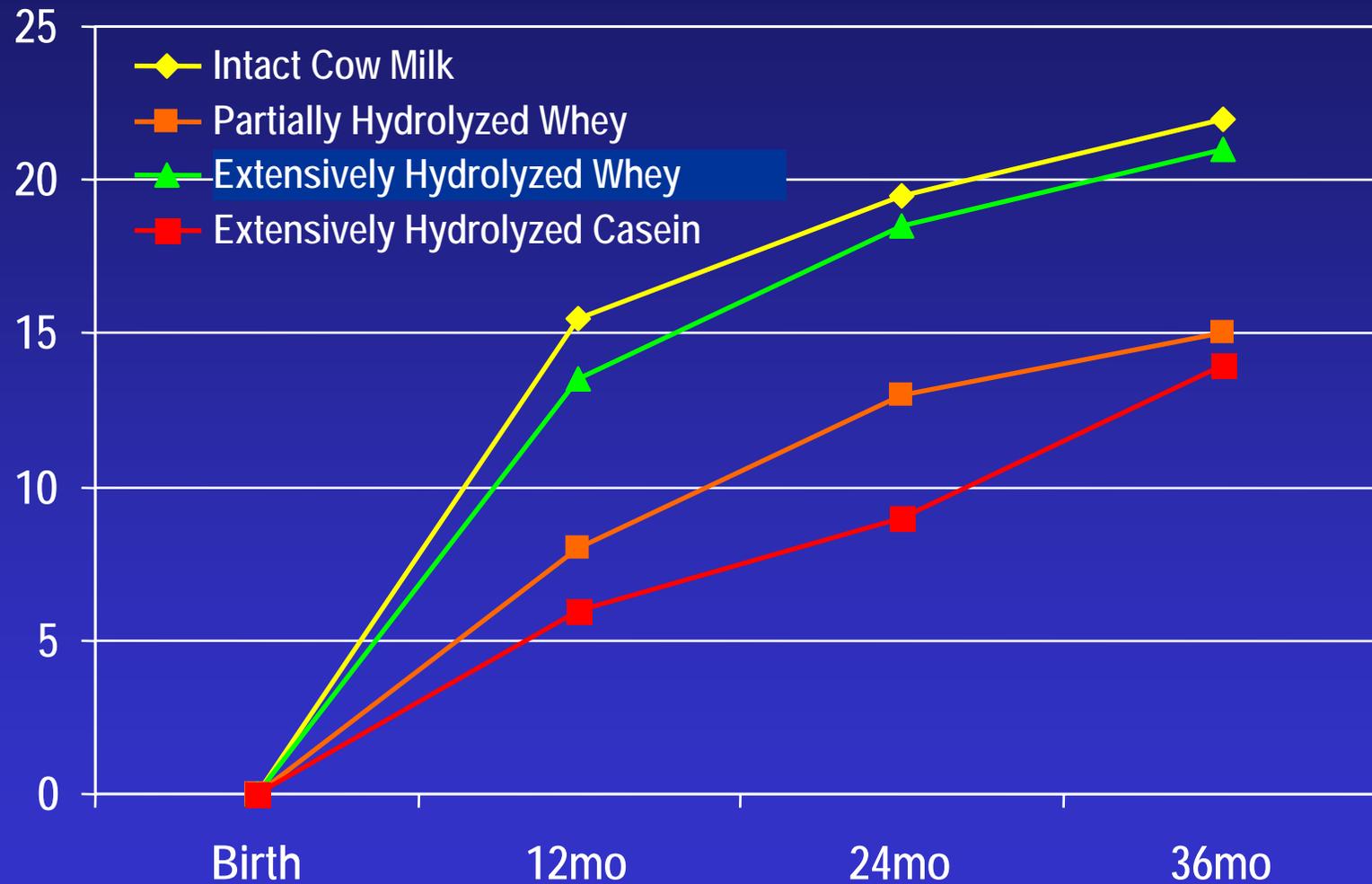


- Graph depicts only published, peer-reviewed, prospective trials with data collection at timepoints >12 months.
- For all studies except Becker 2004, AM includes AD as one of the allergic outcomes assessed; for Becker 2004, AM refers to asthma alone.
- 2 years: Becker 2004, De Seta 1994; 3 years: Marini 1996; 4 years: D'Agata 1996; 5 years: Chandra 1997, Vandenplas 1995
- p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and 95% CI
- Chan 2002 not included. Wheezing reported exclusively, not inclusive of other AM at 30 months.

# The German Infant Nutritional Intervention (GINI) Study

- Independent, government-sponsored study
- 2,252 healthy infants with history of allergy in the family randomized at birth to:
  - Intact cow milk formula vs three hydrolysates
- When not exclusively breast fed, randomized formula was given to 6 mo of age, infants followed up to 12mo
- Incidence of allergic manifestation at 12 months was 13%
  - 89% of all allergic manifestation was atopic dermatitis
- 12 month results published, 3-year publication pending,

# Cumulative Incidence of Atopic Dermatitis



*3 Yr. GINI study : Findings not published. Results presented at ESPACI Meeting, 2003  
Absolute cumulative incidence shown.*

# Meta-Analysis: Formulas containing hydrolysed protein for prevention of allergy

Osborn DA, Sinn J, *The Cochrane Library*, Issue 4, 2003, John Wiley & Sons Ltd.

- Inclusion criteria
  - Randomized trials comparing use of hydrolyzed infant formula to human milk or CMF
  - $\geq 80\%$  follow-up of subjects
  - 18 / 72 studies were eligible for inclusion

# Cochrane Meta-Analysis Conclusions

*“In high risk infants [infants with a positive family history of allergy], who are unable to be completely breast-fed, there is evidence that prolonged feeding with a hydrolysed, compared to cow’s milk formula reduces infant and childhood allergy and infant [cow’s milk allergy].”*

*“Further trials are required to determine if significant clinical benefits persist beyond five years of age and if there is any additional benefit from use of an extensively compared to a partially hydrolysed formula. Incremental costs of formula and the effect on compliance should be measured.”*

# 100% Whey-Protein Partially Hydrolyzed Formula

- Routine use formula
- Palatability comparable to intact protein formulas
- Cost comparable to other brand name routine formulas
- Why is this important?

# Effective Risk Reduction

- Routine use, wide availability
- Acceptable, affordable
- Benefits the population at large

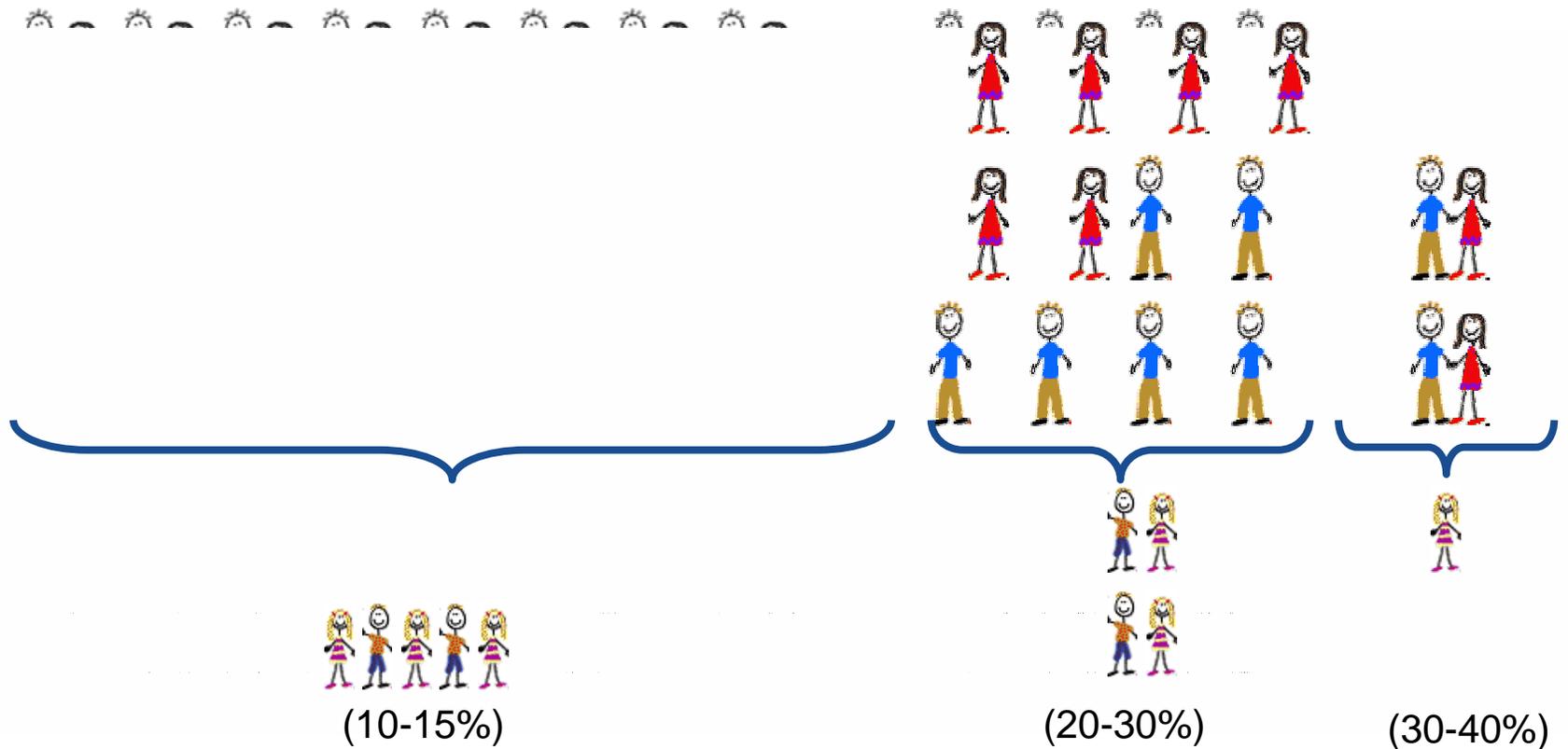
# Prevalence of atopic disease based on parental history

Prevalence of Parental Atopic History:

64% No Parental Hx

31% Uniparental

5% Biparental



## Prevalence of Atopic Disease

Total: 17.6%

9.6%

6.4%

1.6%

Bergman, et al. *Clinical and Experimental Allergy* 1998; 28:905-907

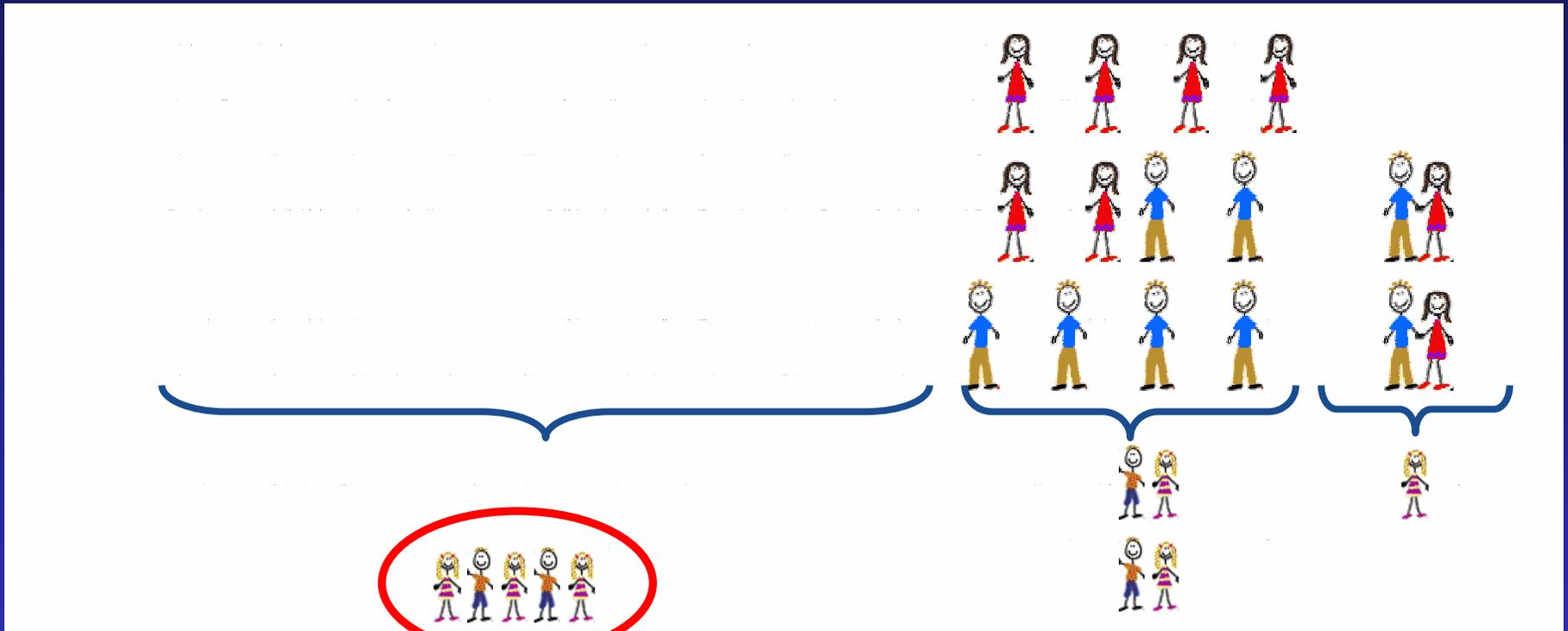
Other refs: Halken S et al. *Allergy* 2000;55: 793-802  
 Bousquet J. et al. *J Allergy Clin Immunol* 1986;78: 1019-1022;  
 Kjellman N. et al. *Acta Paediatr Scan* 1977;66: 565-71  
 Exl BM, *Nutr Res* 2001;21: 355-79

Prevalence of Parental Atopic History:

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Prevalence of Atopic Disease in German Infants (total 17.6%):

9.6%

6.4%

1.6%

> 50% of children who develop allergy do not have a family history

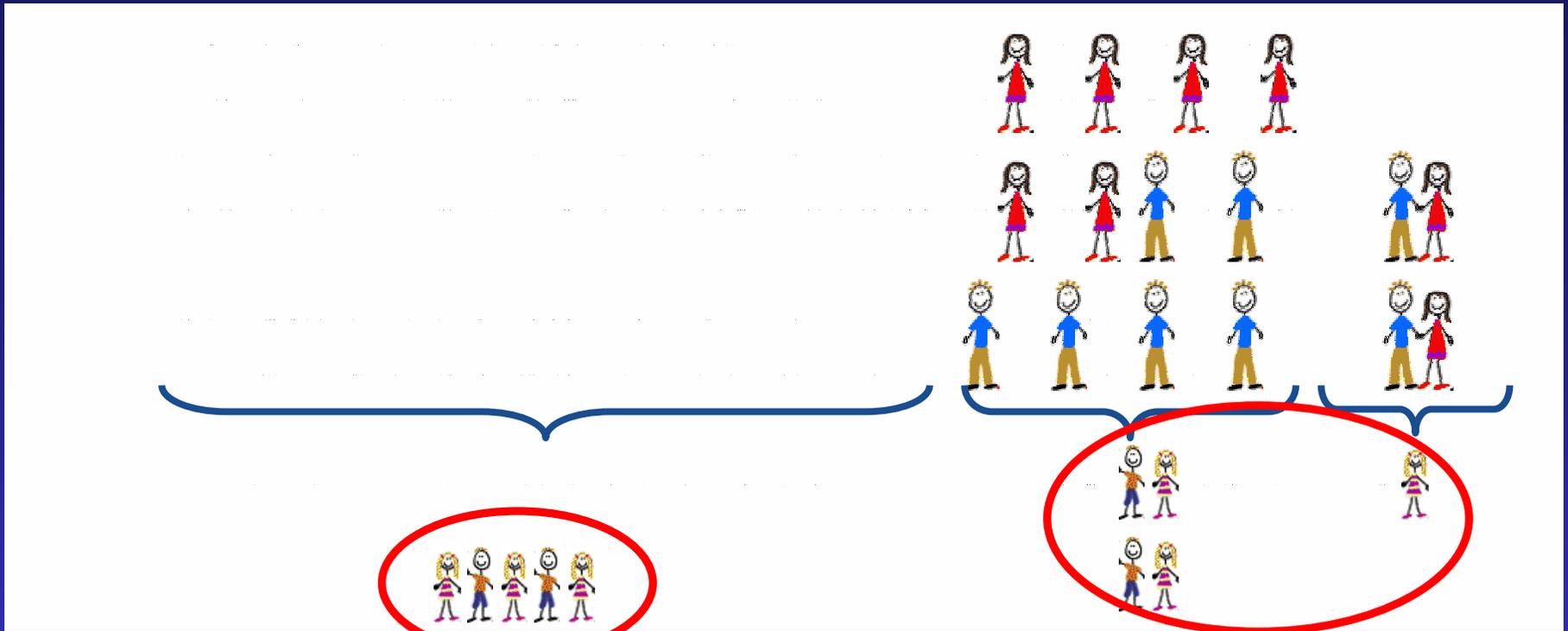
**Most infants at risk for atopy go unidentified**

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Prevalence of Atopic Disease in German Infants (total 17.6%):

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1.6%

> 50% of children who develop allergy do not have a family history

For those who have a family history, there is no mandatory, standardized nor validated mechanism or tool to elicit parental history

**Most infants at risk for atopy go unidentified**

# In Summary: 100% Whey-Protein Partially Hydrolyzed Formulas

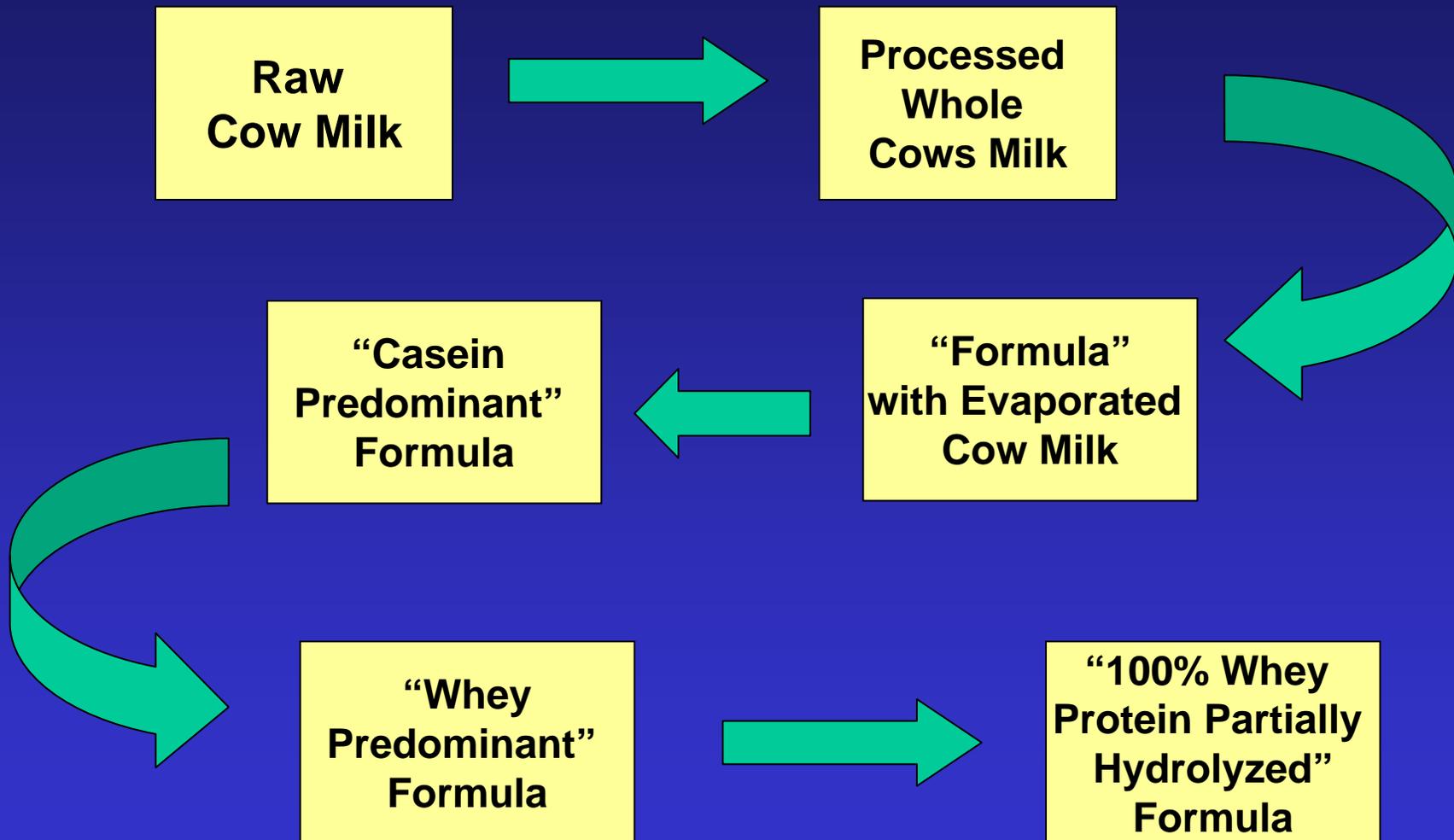
- Well documented role in reduction of the risk of allergy associated to use of intact cow milk protein
- Applicable to the general population
- Safe, Acceptable, Affordable strategy

# Proposed Claim

*“Breastfeeding is the best way to nourish infants. For infants who are not exclusively breastfed, emerging clinical research in healthy infants with family history of allergy shows that feeding a 100% Whey-Protein Partially Hydrolyzed formula may reduce the risk of common food allergy symptoms, particularly allergic skin rash, when used instead of whole-protein cow’s-milk formula from the initiation of formula feeding.*

*Partially hydrolyzed formulas are not intended to treat existing food allergy symptoms. If you suspect your baby is already allergic to milk, or if your baby is on a special formula for the treatment of allergy, your baby's care should be under a doctor’s supervision.”*

# 100% Whey Protein Partially Hydrolyzed: The Latest Generation In Infant Formulas

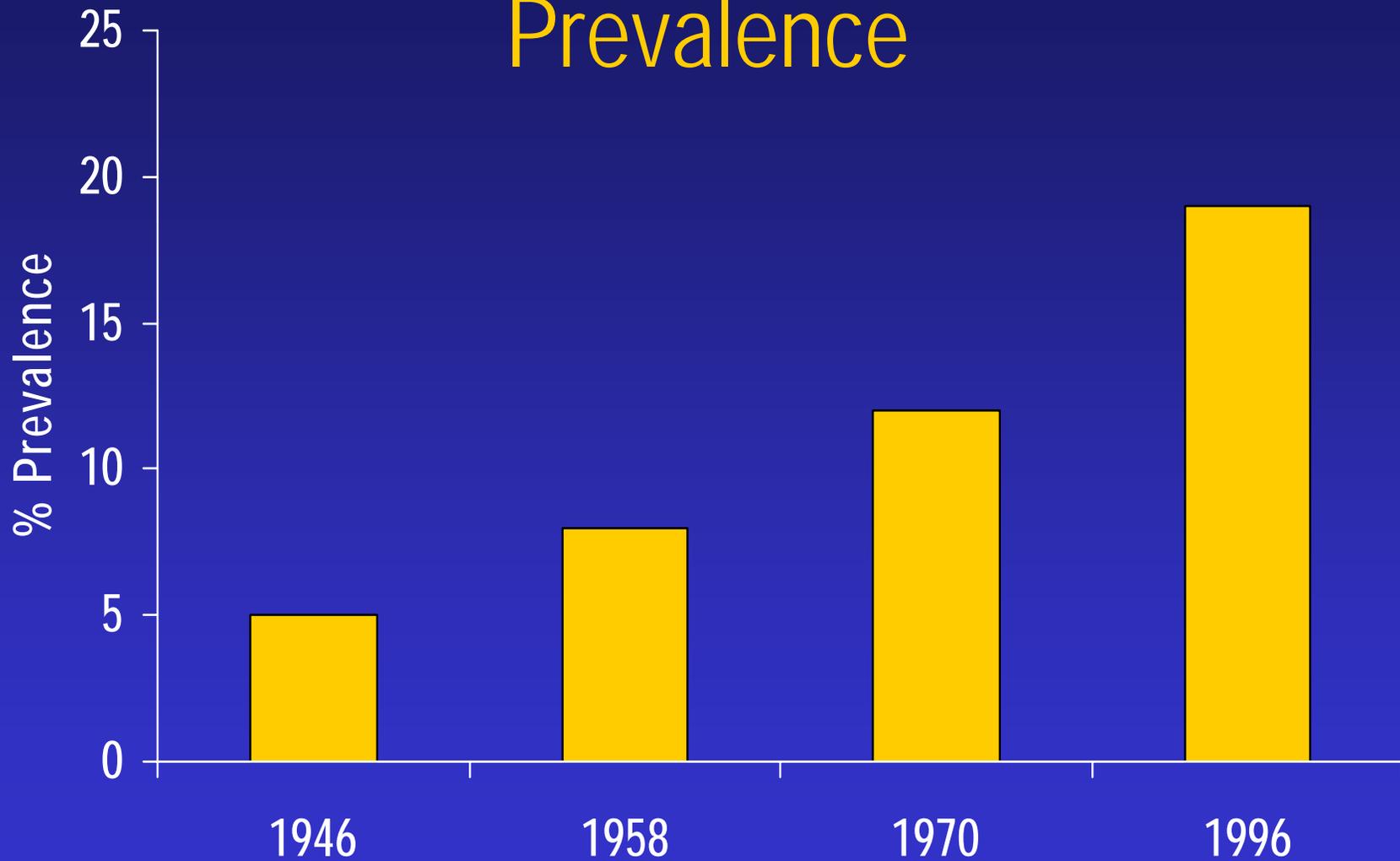


# Addenda: Additional Allergy Background

# Allergy

- Affects as many as 50 million Americans
- Occurs in up to 30% in some populations
  - particularly developed countries
- Leading cause of chronic disease in the U.S.
  - overall - allergies are on the rise
- Food allergy - most common in infants and children

# Trends in Atopic Dermatitis Prevalence



\*Secular trends in the UK  
Eichenfield et al, 2003 *Pediatrics* 111: 608-16

# Atopic Dermatitis: Significance

- Atopic dermatitis in the U.S.
  - Prevalence 10-20% overall<sup>†</sup>
  - Affects 15 million Americans<sup>‡</sup>
  - 17% prevalence by 6 months of age<sup>\*</sup>
  - 7 million visits per year <sup>‡</sup>
- Up to 60% of children with severe atopic dermatitis have food hypersensitivity<sup>\*\*</sup>

<sup>†</sup> NIH- HHS Publication No. 03-4272, Rev April 2003

<sup>‡</sup> CDC Nat Ctr for Health Statistics Vital and Health Statistics Series, 1996, 13:134

<sup>\*</sup> Moore MM - *Pediatrics* - 01-MAR-2004; 113(3 Pt 1): 468-74

<sup>\*\*</sup> Burkes et al. *J Pediatr* 1998, 132(1):132-610

# Allergic March

- Atopic dermatitis may be the first step in the *Allergic March*:  
***the relationship between allergic manifestations throughout life***
  - Approximately 75- 80% of atopic dermatitis patients develop allergic rhinitis
  - More than 50% of atopic dermatitis patients develop asthma

Leung DY - *J Allergy Clin Immunol* - 01-DEC-2003; 112(6 Suppl): S117  
Spergel *J Allergy Clin Immunology* 2003; 112 (6 Suppl): S 118-27

# Increasing Prevalence of Asthma and Atopy

