The Infant Formula Crisis:
What Happened and What's Next?

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Qualifications and Potential Conflicts of Interest

- I was a medical director for Nestle USA and then for Abbott Laboratories in their infant formula businesses over a period of 20 years
- I served as President of the Infant Formula Council
- I'm a retiree of Abbott Laboratories and a stock holder
- I am not a consultant or speaker for any infant formula manufacturer

Infant Formula Shortage

Educational Goals of Presentation

- Be able to describe events leading to the recent (current?) formula crisis
- Be familiar with the role of the FDA in infant formula manufacturing oversight
- Options for formula choices:
  - What if my formula's not on the shelf?
- What can be done to prevent another formula shortage

But First…
An Infant Formula Anecdote

- In Los Angeles in 1975, a pediatric resident admitted an infant from an ER with generalized edema with obvious nephrotic syndrome.
- The next morning, this resident became the senior resident on the floor where the child was admitted.
- The urinalysis, obtained later that night, had came back, what? Normal!!!
- He got back to basics and took a history. He learned, on physician advice, the child had been fed milk free Mocha Mix dairy creamer to treat suspected milk allergy.
- The infant had kwashiorkor. He was treated and cured with resumption of a standard infant formula.
- The resident's subsequent career was largely set in motion by that late night admission. Here I am today, almost 50 years later, still talking about nutrition and infant formula!

Why Infant Formula?

- ”There will always be a need[1]”
  - Maternal illness, separation, death
  - Choice not to breast feed
  - Breastmilk insufficiency
- Current formula usage by infants[2]
  - 16% from birth
  - More than 50% receive some formula by 3 months
  - >75% have receive at least some formula by 1 year

[1]Baker RD 2016
[2]AAP Pediatric Nutrition Handbook

The US Infant Formula Marketplace

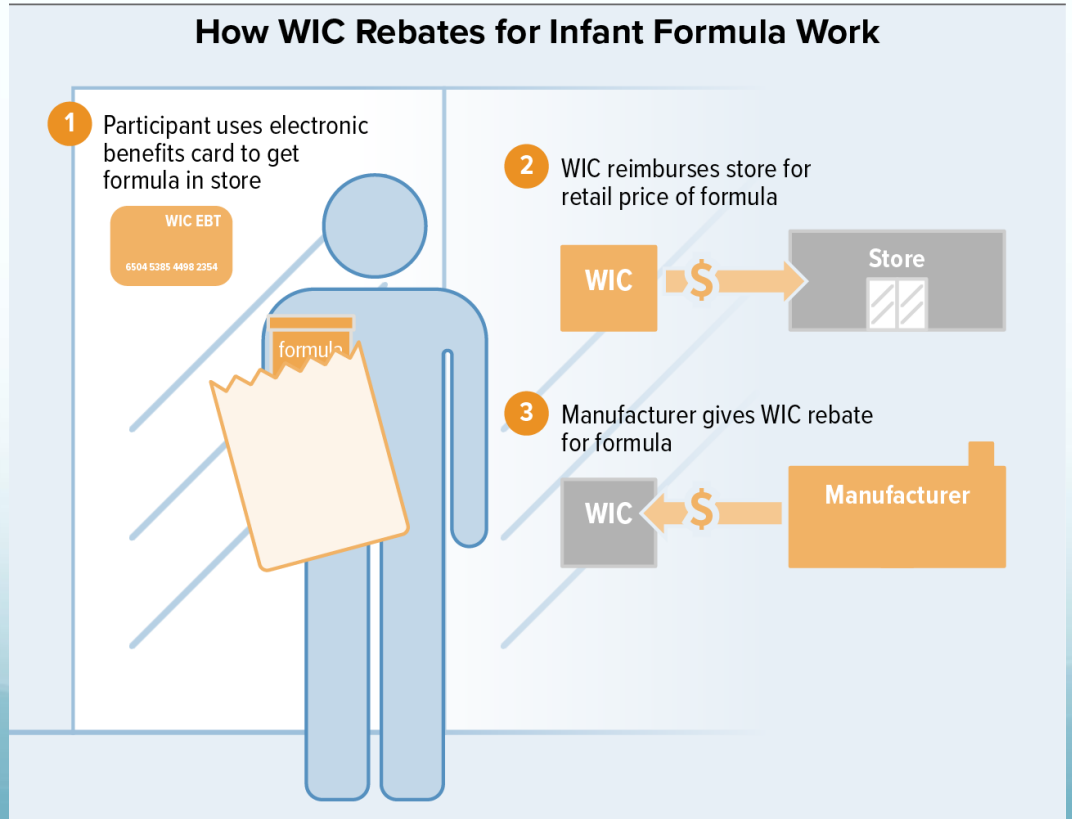
- 5 infant formula manufacturers; 4 have >90% of the US market
- 1-3 domestic manufacturing plants per company
- Over 200 million powder pounds equivalent sold yearly for 3 million infants who are receiving formula at any time
- ~60% is WIC-driven: powder and concentrated liquid (CL)
- More than 60% of US formula is powder
- Consumer cost:
  - RTF>CL>powder;
  - Special formulas>standard formulas;
  - Major brands>store brands (all made by 1 manufacturer)>WIC

Infant Formula Economics

- Not a growing market
  - Falling birth rate (except pandemic year)
  - Long term trend towards more breast feeding
  - Retail prices rising faster than inflation
- Almost exclusively a domestic market (~98%)
  - High tariffs & exclusion of formulas from free trade agreements
  - Challenging FDA regulations and labeling for manufacturers, including annual inspections
- Highly concentrated market
  - High cost of entry
    - Last new entrant reportedly spent 190 M over 5 years to bring 1 formula to market
- WIC (USDA) contracts play a huge role in shelf space and market share. WIC buys >half of US infant formula
  - Only 3 manufacturers bid
  - Volume required and high rebates are another barrier to competition
  - WIC contracts have a major impact on non-WIC market share

WIC Contracts

- Each state, (or groups of states) territory & tribal area annually opens a blind bid for a single WIC contract
- The company offering the largest rebate wins the contract
- Contract covers standard powdered formula and concentrated liquid
- The rebate can exceed 90% of the retail cost
- Rebated funds are used to expand WIC access
- WIC typically covers about 70% of an infant's monthly formula



What led to the 2022 Shortages?

The Dwindling Formula Pipeline

Pre-pandemic

2020

Pandemic Shipping Slowdown

February 2022

Plant closure

Winter-Spring 2022

Hoarding

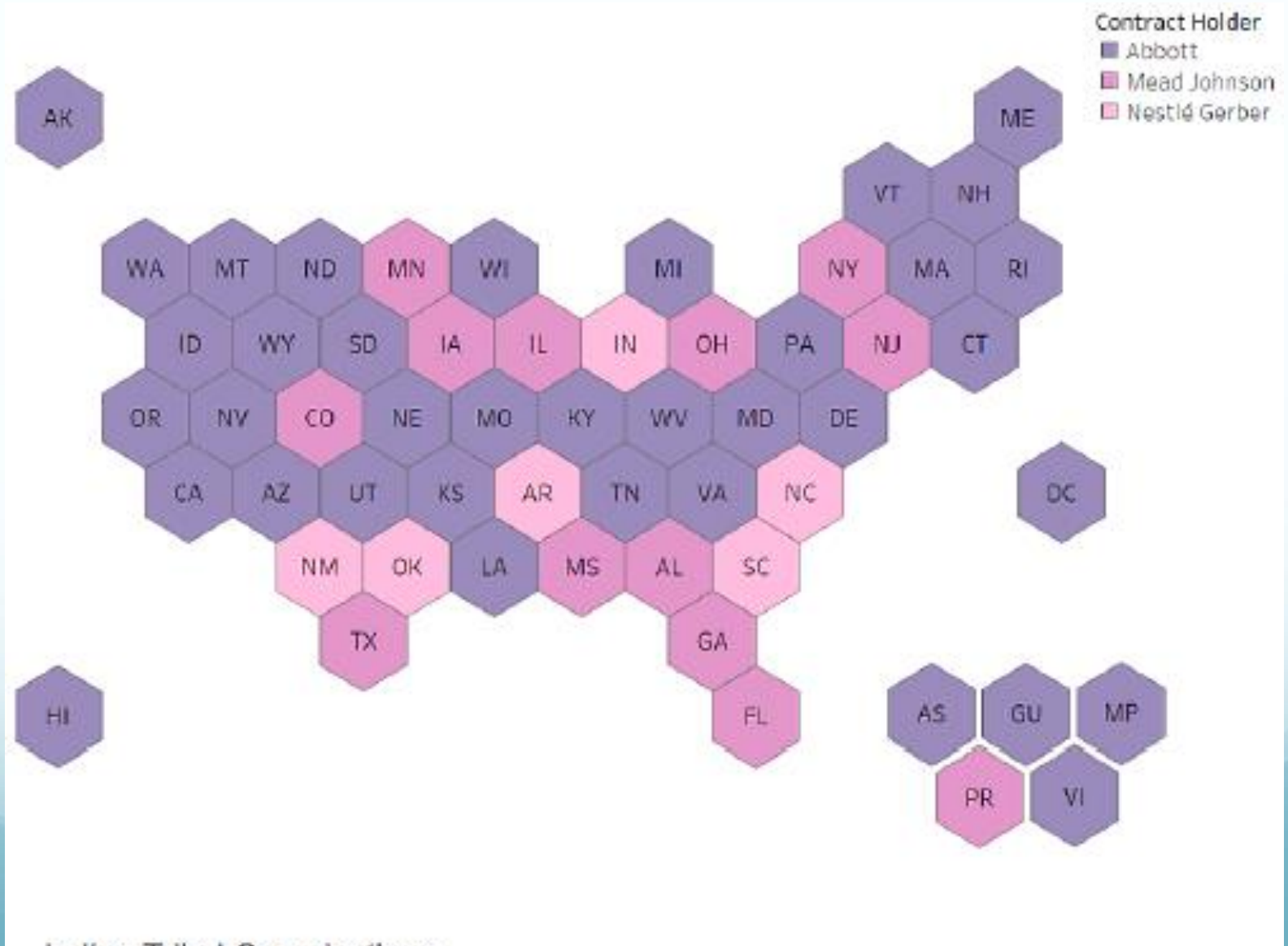
June 2022

Flood

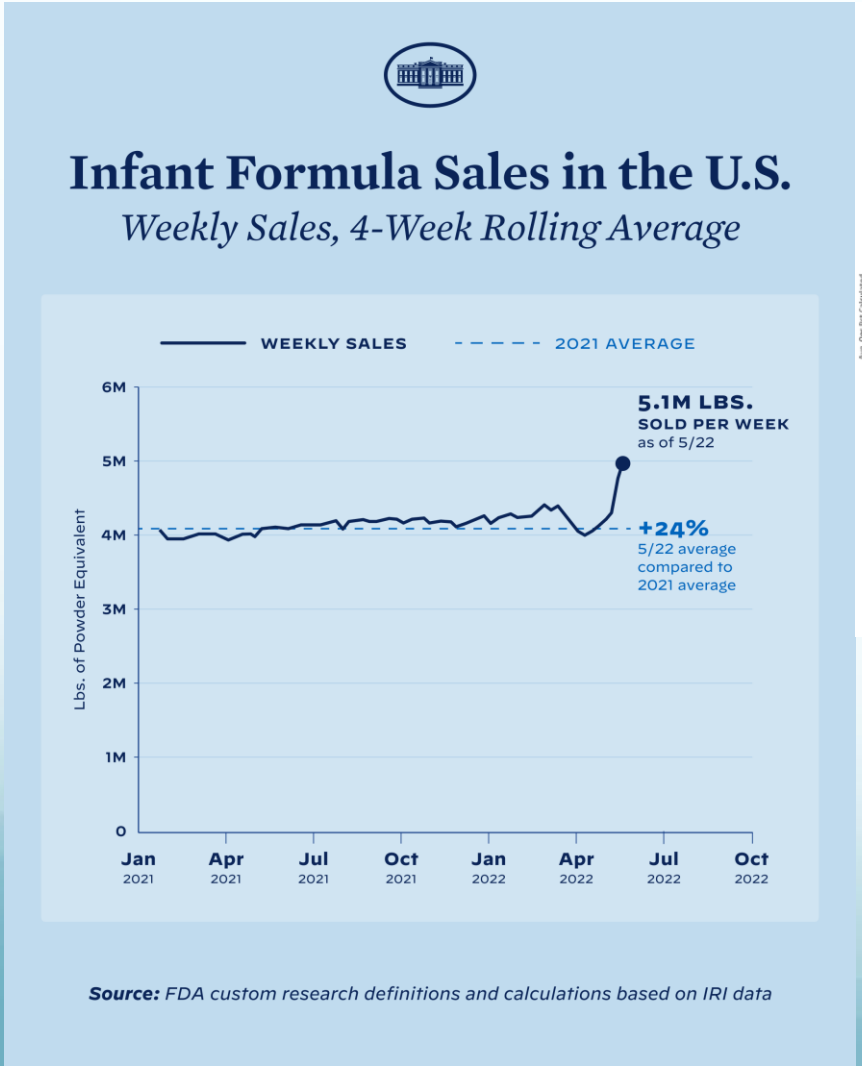
How the Formula Shortage Grew

- Stress mode to crisis mode
  - Abbott Laboratories announced infant formula recalls on February 17 and 28, 2022. They stopped production at their manufacturing plant in Sturgis, MI
- Why did this have such an impact?
  - Abbott had a high percentage of the WIC contracts
  - The plant was a major source of powdered formula and specialty formulas for infants and children with food allergies, severe GI disorders and inborn errors of metabolism
  - There was little formula in reserve and limited idle manufacturing capacity to activate, especially for specialty products
- How did consumers respond? They bought more formula
- The infant formula shelves went progressively bare February thru June
- Initially, European formulas could not be imported due to FDA regulations
- The government response to emerging shortages was not immediate

WIC Contracts in 2022



Empty Shelves 2022



FDA Role

- In person FDA inspections of the Sturgis, MI plant not done due to pandemic related constraints 2019-2021
- An inspection in September, 2021 found evidence of un-hygienic practices
- FDA received a former employee whistleblower complaint in October, 2021 claiming unsafe practices This was not escalated within the agency.
- 3 cases of C sazakaii were reported to CDC Sept 21-Jan 22 in infants consuming Sturgis powdered formulas
- A repeat inspection in January/February 2022 confirmed September findings. Environmental samples were positive for C sakazakii and batch records showed evidence of destruction of possibly contaminated product. The recalls and plant shut down ensued

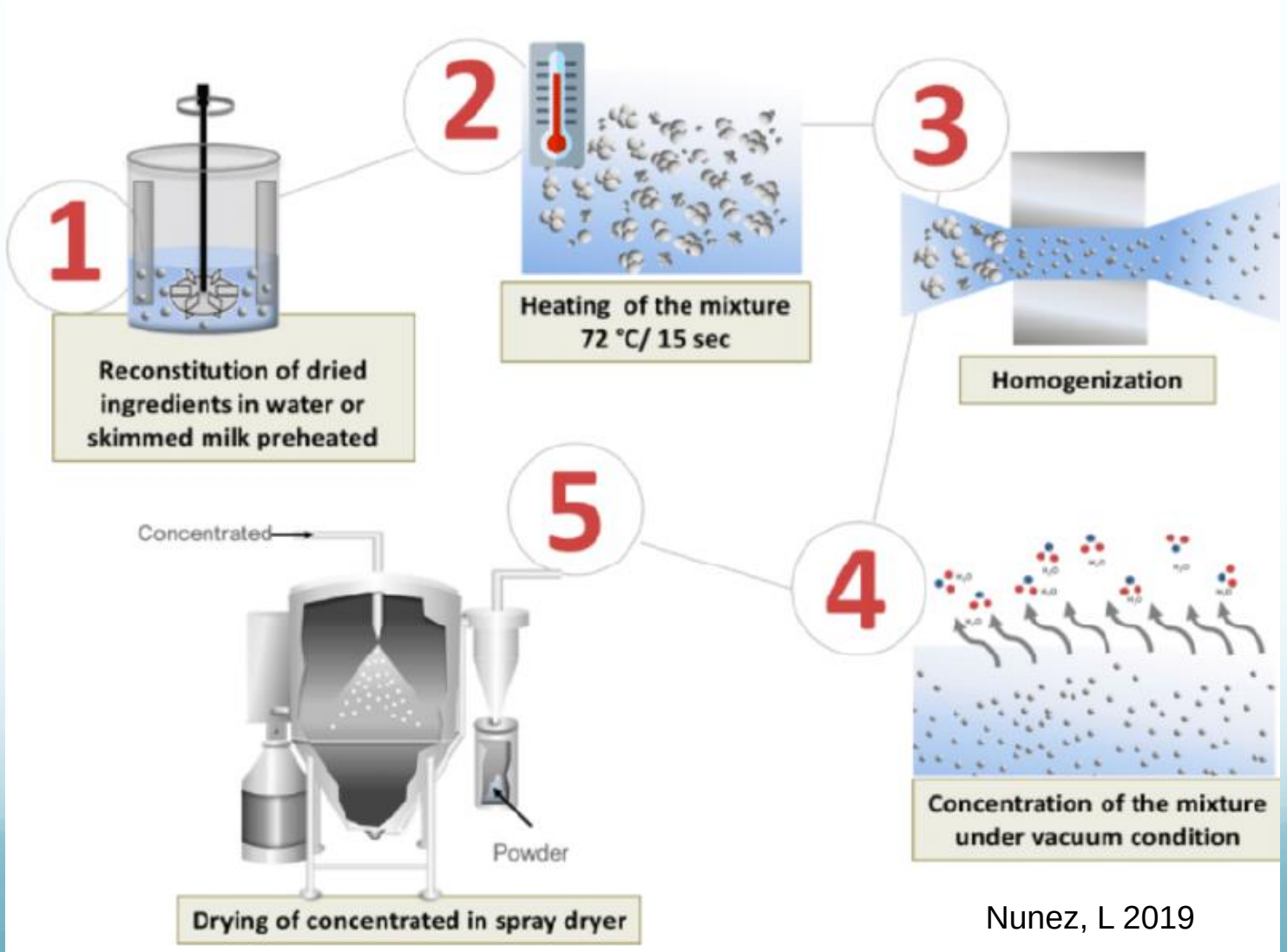
How FDA Regulates Infant Formula

- The Center for Food Safety and Applied enforces the Infant Formula Act
- FDA does not “approve” new or modified infant formulas for marketing, but is empowered to initiate regulatory action for adulterated or mislabeled products
- Enforces “quality factors” for infant formula
  - Protein quality (Protein Efficiency Ratio; PER)
  - Assurance of healthy growth (4 month growth study)
- Enforces Good Manufacturing processes
  - Is there a procedure for each step and is it followed?
- Requires testing of all formula batches for nutrient minima (30) and maxima (10) and microbes including Salmonella and Cronobacter
- Inspects manufacturing plants at least annually
- Reviews production records and mandated complaint monitoring files
- Issues “483” citations for manufacturing deficiencies and monitors for their correction

FDA's Internal Postmortem: Formula Shortage

- Lack of modern systems for managing product and whistleblower complaints and for shipping and testing formula
- Limited emergency response capability
  - No remote monitoring capability during pandemic
  - Poor systems for coordinating with other agencies
- Insufficient personnel (and training) to meet responsibilities, e.g., infant formula plant inspections
- Insufficient policies to hold industry responsible for modern data management systems and an appropriate safety culture
- Insufficient engagement with other stakeholders and agencies related to food safety and management of C Sakazakii

Manufacturing Process:
Powdered Infant Formula



Nunez, L 2019

Powder Dryer

Powdered infant formula is not sterile—no terminal sterilization process

Terminal Sterilization of RTF and Concentrated Liquid

Beverage Industry
Website 5/14/2018

Retort sterilizer

Aseptic filler

Why C. sakazakii Testing?

- Ubiquitous organism in soils and food products, and even breast pumps
  - Can enter formula anywhere from manufacturing plant to bottle
- Causes rare severe infections in young infants and immunocompromised patients
  - NEC, sepsis, & meningitis with high fatality rate and potential for severe residual morbidities
- Most common etiologic association is with POWDERED infant formula; survives in low water environments and can grow rapidly when rehydrated
- Infant formula plant environmental and batch testing required since 2014
- No national case reporting system; only Minnesota mandates reporting
- FDA and CDC: consider RTF formulas for infants < 2 months of age, premies and immunocompromised and possibly using hotter water to prepare powdered formula for these subgroups
- At least 3 other manufacturers have issued recalls for C sakazakii risk since the February 2022 plant shutdown

My baby's formula is not on the shelf: What now?

1. Panic, scream, complain, cry
2. Blame the big corporations and the government
3. Open my web browser

   But who can I trust?
   - Government agencies?
   - Professional groups?
   - Infant formula manufacturers?
   - News media?
   - Facebook and Twitter?
   - Consumer advocates?
   - New local peer groups?
   - Parent blogs?
4. Take a deep breath
5. Call my doctor

Appropriate responses

- All of the above…
- As consumers, we have limited patience and lots of frustration with product shortages
- There is plenty of blame here for corporations and government
- Lots of information became available, some of it useful, a little of it dangerous
- Families need a guide to get through the shortage:
  - You, their doctor or health care professional

Impact of Shortages

- For Health Care Providers
- Changes in practice
  - Earlier transition off special formula
  - Management of intolerance of new formula
- Workload issues
  - More calls, office visits
  - Attempts to aid patients find formula
  - Need to develop more expertise for formula guidance

For Families & Caretakers

- Need to find alternative formula--NOW
- Intolerance, weight loss and malnutrition issues with some substitutes
- Equity aspects—disparities in access to available formula
- Loss of faith in formulas, FDA and authorities
- Frustration and anxiety—*How can I feed my child?*
- Healthcare utilization
  - Increased visits to office, clinics, hospitalizations

Adapted from Sentongo T et al 2022

Smart Shopping

- Look in other neighborhoods
- Look in other kinds of stores
- Find local parent networks
- Call a friend who lives in a different community or state
- Get ideas from your HCP
- Avoid hoarding of infant formula

And How Will You Help?

- Important to have knowledge of formulas, their uses and the local community and professional resources
- Formula assessment
  - How special is the current formula?
  - Look for similar options—consider other brands of same type—see NASPGHAN list
  - Use of another form of product (RTF or concentrated liquid)
  - What else might work?
  - Parents who have unused formula may want to share
- Special factors for this child and mother
  - How old is the infant?
  - Strength of evidence a special formula is (still) needed
  - Finances and WIC
- Provide advice re: reliable sources of information
- Utilize personal contacts with manufacturer and its representatives
- Advocacy with manufacturer, insurance, WIC, DME provider

Grey Areas

- Age when milk can be fed in lieu of formula
- Use of toddler products in older infants
- Use of recently outdated formula
- Ordering a formula approved for use in Europe on the internet

Sources of Information

- Professional society websites
  - AAP
  - Academy of Nutrition and Dietetics
  - NASPGHAN (alternative formulas)
- Government websites
  - The White House
  - CDC
  - FDA
  - WIC, USDA and the local WIC office
- Infant formula manufacturers' websites
- Local and regional stores

How Different are European Formulas?

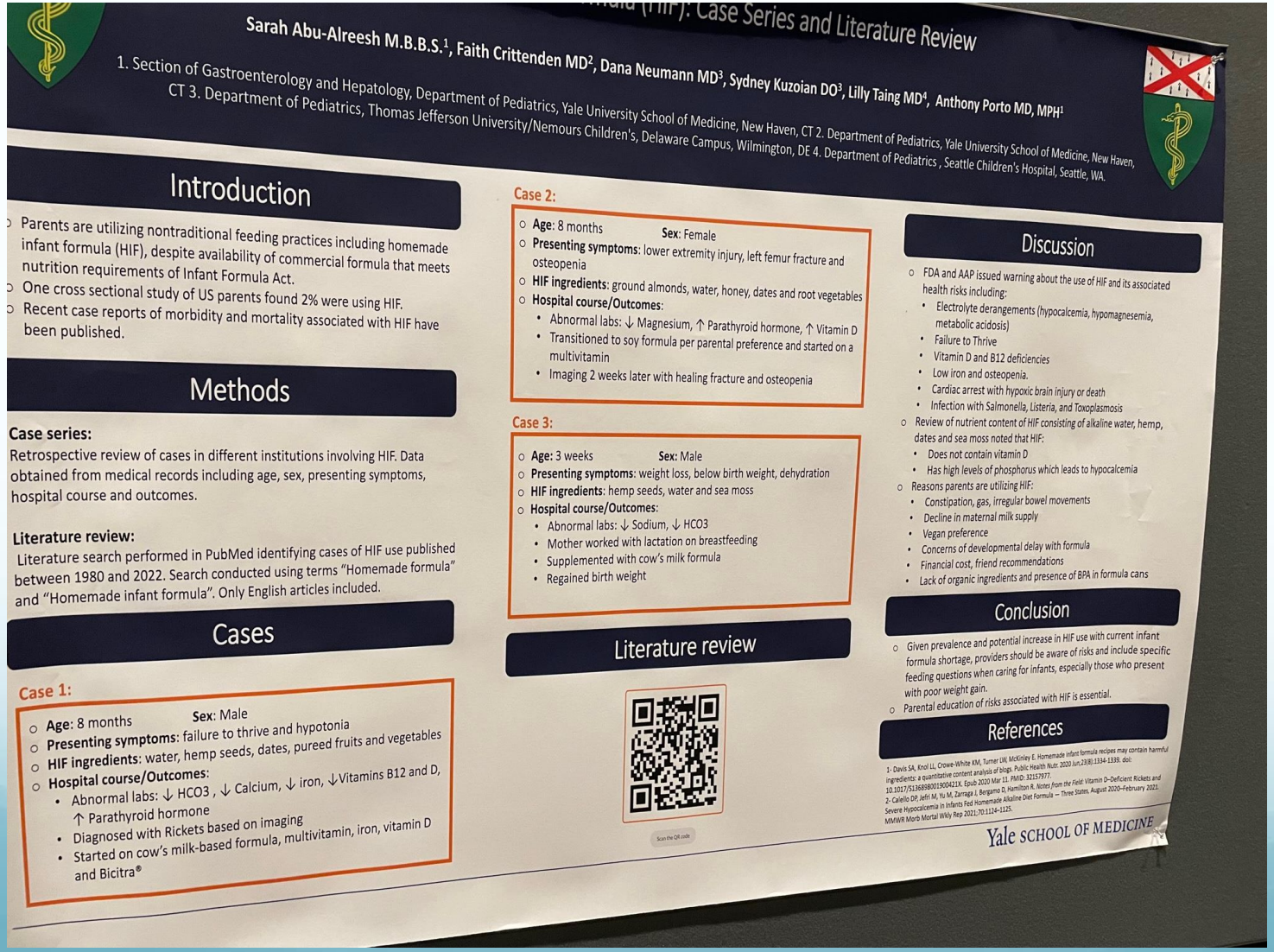
- Ingredients basically the same, sourced from some of the same suppliers
- Marketing emphasis often on “purity”
- Staged system for formulas (<6months>)
- Small differences in the functional ingredients added
- E.U Formula final product nutrient testing less stringent
- Labeling and units for nutrient or formula and preparation may differ (average content vs minimum content)
- Most nutrient levels comply with FDA regulations; others are close

See DiMaggio DM, 2019

What Caretakers Should Not Do

- Dilute formula to make it last longer
- Stop using a specialized formula prescribed for a diagnosed medical problem without MD consultation
- Substitute cow or goat milk (unless approaching 1 year of age)
- Substitute a plant based milk other than soy formula
- Use someone else's breast milk (unless from a milk bank)
- Make their own formula

Homemade Formulas are Still Being Concocted with Disastrous Results



Case Series and Literature Review

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Introduction

- Parents are utilizing nontraditional feeding practices including homemade infant formula (HIF), despite availability of commercial formula that meets nutrition requirements of Infant Formula Act.
- One cross sectional study of US parents found 2% were using HIF.
- Recent case reports of morbidity and mortality associated with HIF have been published.

Methods

Case series:

Retrospective review of cases in different institutions involving HIF. Data obtained from medical records including age, sex, presenting symptoms, hospital course and outcomes.

Literature review:

Literature search performed in PubMed identifying cases of HIF use published between 1980 and 2022. Search conducted using terms "Homemade formula" and "Homemade infant formula". Only English articles included.

Cases

Case 1:

- **Age**: 8 months **Sex**: Male
- **Presenting symptoms**: failure to thrive and hypotonia
- **HIF ingredients**: water, hemp seeds, dates, pureed fruits and vegetables
- **Hospital course/Outcomes**:
  - Abnormal labs: ↓ HCO3 , ↓ Calcium, ↓ iron, ↓Vitamins B12 and D, ↑ Parathyroid hormone
  - Diagnosed with Rickets based on imaging
  - Started on cow's milk-based formula, multivitamin, iron, vitamin D and Bicitra®

Case 2:

- **Age**: 8 months **Sex**: Female
- **Presenting symptoms**: lower extremity injury, left femur fracture and osteopenia
- **HIF ingredients**: ground almonds, water, honey, dates and root vegetables
- **Hospital course/Outcomes**:
  - Abnormal labs: ↓ Magnesium, ↑ Parathyroid hormone, ↑ Vitamin D
  - Transitioned to soy formula per parental preference and started on a multivitamin
  - Imaging 2 weeks later with healing fracture and osteopenia

Case 3:

- **Age:** 3 weeks **Sex:** Male
- **Presenting symptoms**: weight loss, below birth weight, dehydration
- **HIF ingredients**: hemp seeds, water and sea moss
- **Hospital course/Outcomes**:
  - Abnormal labs: ↓ Sodium, ↓ HCO3
  - Mother worked with lactation on breastfeeding
  - Supplemented with cow's milk formula
  - Regained birth weight

Literature review

Scan the QR code

Discussion

- FDA and AAP issued warning about the use of HIF and its associated health risks including:
  - Electrolyte derangements (hypocalcemia, hypomagnesemia, metabolic acidosis)
  - Failure to Thrive
  - Vitamin D and B12 deficiencies
  - Low iron and osteopenia.
  - Cardiac arrest with hypoxic brain injury or death
  - Infection with Salmonella, Listeria, and Toxoplasmosis
- Review of nutrient content of HIF consisting of alkaline water, hemp, dates and sea moss noted that HIF:
  - Does not contain vitamin D
  - Has high levels of phosphorus which leads to hypocalcemia
- Reasons parents are utilizing HIF:
  - Constipation, gas, irregular bowel movements
  - Decline in maternal milk supply
  - Vegan preference
  - Concerns of developmental delay with formula
  - Financial cost, friend recommendations
  - Lack of organic ingredients and presence of BPA in formula cans

Conclusion

- Given prevalence and potential increase in HIF use with current infant formula shortage, providers should be aware of risks and include specific feeding questions when caring for infants, especially those who present with poor weight gain.
- Parental education of risks associated with HIF is essential.

References

1- Davis SA, Knoll LL, Crowe-White KM, Turner LW, McKinley E. Homemade infant formula recipes may contain harmful ingredients: a quantitative content analysis of blogs. Public Health Nutr. 2020 Jun;23(8):1334-1339. doi: 10.1017/S1368980019004211X. Epub 2020 Mar 11. PMID: 32157977.

2- Calello DP, Jefri M, Yu M, Zarraga J, Bergamo D, Hamilton R. Notes from the Field: Vitamin D–Deficient Rickets and Severe Hypocalcemia in Infants Fed Homemade Alkaline Diet Formula — Three States, August 2020–February 2021. MMWR Morb Mortal Wkly Rep 2021;70:1124–1125.

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Special Formulas

Infants needing special formulas may suffer severe consequences if switched to a standard formula

Intended use

- Premature infants
- Milk allergy
- Short bowel syndrome or malabsorption
- Inborn errors of metabolism

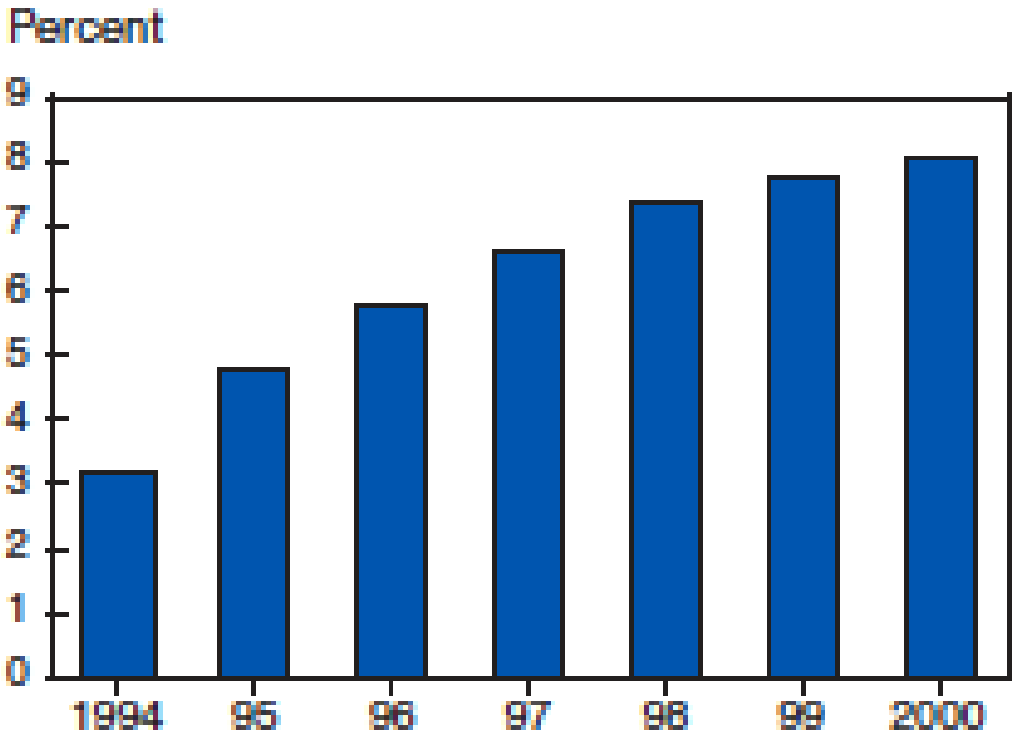
Formula modification

- High nutrient density
- Hypoallergenic
- Modified fat, protein and carbohydrate for better absorption
- Specific nutrient avoidance, modification and addition

Special Formula Use

Figure 6-5

Specialized infant formula as a percentage of all infant formula sold in the United States



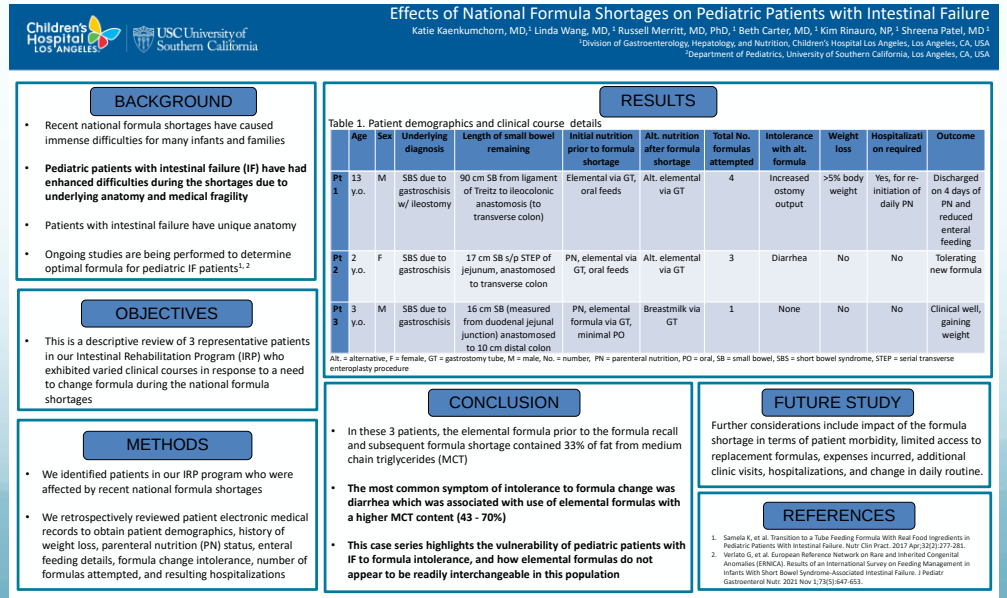
Source: ERS analysis of InfoScan data.

Why were Special Formulas Problematic?

- Most are powdered formulas
- Few manufacturers make them; many unique
- The elemental infant formula & up age product with dominant market share, as well as many metabolic formulas, were powder formulas made at Sturgis
- Children, as well as infants, are dependent on some of these special formulas
- It's not feasible to begin manufacturing such a specialized product (e.g., elemental, hypoallergenic) without a long lead time and clinical testing

Not All Special Formulas Are Created Equal

- Variable response observed to change in elemental formula
- Often multiple formulas needed to be tried
- Some patients experienced intolerance, diarrhea and progressive weight loss requiring hospitalization
- Differences in amount of MCT oil may be related to tolerance issues



Effects of National Formula Shortages on Pediatric Patients with Intestinal Failure

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BACKGROUND

- Recent national formula shortages have caused immense difficulties for many infants and families
- **Pediatric patients with intestinal failure (IF) have had enhanced difficulties during the shortages due to underlying anatomy and medical fragility**
- Patients with intestinal failure have unique anatomy
- Ongoing studies are being performed to determine optimal formula for pediatric IF patients[1, 2]

OBJECTIVES

- This is a descriptive review of 3 representative patients in our Intestinal Rehabilitation Program (IRP) who exhibited varied clinical courses in response to a need to change formula during the national formula shortages

METHODS

- We identified patients in our IRP program who were affected by recent national formula shortages
- We retrospectively reviewed patient electronic medical records to obtain patient demographics, history of weight loss, parenteral nutrition (PN) status, enteral feeding details, formula change intolerance, number of formulas attempted, and resulting hospitalizations

RESULTS

Table 1. Patient demographics and clinical course details

	Age	Sex	Underlying diagnosis	Length of small bowel remaining	Initial nutrition prior to formula shortage	Alt. nutrition after formula shortage	Total No. formulas attempted	Intolerance with alt. formula	Weight loss	Hospitalization required	Outcome
Pt 1	13 y.o.	M	SBS due to gastroschisis w/ ileostomy	90 cm SB from ligament of Treitz to ileocolonic anastomosis (to transverse colon)	Elemental via GT, oral feeds	Alt. elemental via GT	4	Increased ostomy output	>5% body weight	Yes, for re-initiation of daily PN	Discharged on 4 days of PN and reduced enteral feeding
Pt 2	2 y.o.	F	SBS due to gastroschisis	17 cm SB s/p STEP of jejunum, anastomosed to transverse colon	PN, elemental via GT, oral feeds	Alt. elemental via GT	3	Diarrhea	No	No	Tolerating new formula
Pt 3	3 y.o.	M	SBS due to gastroschisis	16 cm SB (measured from duodenal jejunal junction) anastomosed to 10 cm distal colon	PN, elemental formula via GT, minimal PO	Breastmilk via GT	1	None	No	No	Clinical well, gaining weight

Alt. = alternative, F = female, GT = gastrostomy tube, M = male, No. = number, PN = parenteral nutrition, PO = oral, SB = small bowel, SBS = short bowel syndrome, STEP = serial transverse enteroplasty procedure

CONCLUSION

- In these 3 patients, the elemental formula prior to the formula recall and subsequent formula shortage contained 33% of fat from medium chain triglycerides (MCT)
- **The most common symptom of intolerance to formula change was diarrhea which was associated with use of elemental formulas with a higher MCT content (43 - 70%)**
- **This case series highlights the vulnerability of pediatric patients with IF to formula intolerance, and how elemental formulas do not appear to be readily interchangeable in this population**

FUTURE STUDY

Further considerations include impact of the formula shortage in terms of patient morbidity, limited access to replacement formulas, expenses incurred, additional clinic visits, hospitalizations, and change in daily routine.

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1. Samela K, et al. Transition to a Tube Feeding Formula With Real Food Ingredients in Pediatric Patients With Intestinal Failure. Nutr Clin Pract. 2017 Apr;32(2):277-281.
2. Verlato G, et al. European Reference Network on Rare and Inherited Congenital Anomalies (ERNICA). Results of an International Survey on Feeding Management in Infants With Short Bowel Syndrome-Associated Intestinal Failure. J Pediatr Gastroenterol Nutr. 2021 Nov 1;73(5):647-653.

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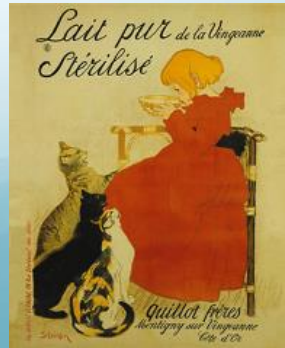
Steps Taken by Federal Government

- FDA
  - Metabolic formulas from the affected plant were released
  - Allowed importation of selected formulas
- White House
  - Defense Production Act activation for ingredients May 18, 2022
  - Operation Fly May 18, 2022 to import formulas
  - Worked with key stakeholders including AAP and NASPGHAN
  - At White House request, most state WIC offices modified policies to allow non-contracted formula purchase
  - Conference on Hunger, Nutrition and Health (AAP included)
- Multi-agency
  - information websites launched
- Congress
  - passed the Access to Baby Formula Act to increase WIC flexibility during disasters and COMPETES act to stimulate business development
  - Held hearings re: FDA and Abbott

Suggested Interventions to Reduce C sakazakii infection risk

- Routinely feed infants < 2 months, premature infants and immunocompromised patients RTF formula, as per CDC and FDA guidance. Maybe use hot water in formula preparation
- National reporting requirement for C Sakazakii infections
  - Standardize investigation of cases, as CDC has for SIDS
- Staff up FDA to enforce IFA regulations and inspect plants regularly
- Develop new methods to reduce powdered formula risk
  - Testing methods and protocols
  - Processing innovations and additions
    - Many methods and ingredients being investigated



Suggested Interventions to Reduce Likelihood of Future Shortages

- Establish a rotating stockpile of critical formulas
- Require >1 plant to manufacture critical formulas
- Implement standing changes to WIC and SNAP rules to allow flexibility to provide non-contracted formulas
- Make it easier to import high quality formulas; reduce trade barriers
- Limit product recalls to at risk populations through professional and consumer education
- More effective FDA oversight by congress
- Require hospitals, insurance companies and DME providers supply alternate (noncontracted) formulas, when there is a shortage

Longer term Interventions

- Continue to encourage higher rate of breastfeeding initiation and longer duration of breastfeeding
  - WIC coverage of lactation counseling and breast pumps
  - Workplace lactation support and paid parental leave
- Support wider availability of donor milk
- Examine alternatives to sole source WIC bidding that won't shrink WIC formula availability
- Explore incentives for new infant formula manufacturers to enter the market with shorter FDA review times
- Develop a more robust, coordinated crisis management system at FDA and other federal agencies
- Congress needs to pass the Nutrition Equity Act

Future Infant Formula Development

[1]Deckelbaum RJ, 2004
[2]Benson & Masor, 1994
[3]Munblit D, 2020

- Research framework
  - FDA and Infant Formula Act define mandated formula composition and testing
  - Approaches for assuring safety of new Ingredients described[1]
  - Models: Human milk and health of breast fed baby, especially ingredients in human milk thought to confer benefit[2]

- Manufacturer Interest and much research investment:
  - Neurodevelopment
  - Immune support and infectious disease prevention
    - Includes human milk oligosaccharides
  - Allergy prevention
  - Precision fermentation of proteins
  - Healthy microbiome development
  - Nutritional epigenetics
  - Obesity prevention
  - Environmentally sensitive packaging

- Any health claims resulting from new ingredients or devices should be well-supported by high quality clinical studies to protect consumers[3]

A Few Take Aways

- Encourage as much breast feeding as possible for as long as possible
- Powdered infant formula is not sterile
- Use RTF formula for high risk infants
- A solid understanding of types of formulas and their indications will lead to selecting an appropriate alternative when one is in short supply
- Work strategically and supportively when helping parents search for a preferred formula
- There's lots of help out there—professional societies, government agencies and manufacturers—contact them!
- Your voice can help bring needed policy changes to assure the consistent availability of safe infant formulas.