The Neonatal Group B Streptococcal Epidemic: Lessons Learned from Studying Associations

Commentary on A.Q. Ismail et al.: Cow's Milk and the Emergence of Group B Streptococcal Disease in Newborn Babies (Neonatology 2011;100:404–408)

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Ismail et al. [1] report a temporal relationship between the onset of neonatal infections caused by the group B streptococcus (GBS) in the UK and changes in milk processing on dairy farms. The collection of bovine milk changed from churns to bulk tanks between 1960 and 1979, a time frame that nearly coincides with the onset and pinnacle of the neonatal GBS epidemic. The authors further propose this temporal change in milk processing supports the concept that human GBS pathogens are derived from a bovine ancestor.

Literature reports on interesting associations only rarely prove ultimately to be causal [2]. In his classic article on etiologic epidemiology, Sir Austin Bradford Hill [3] offered his viewpoints wherein an association might be considered causal. His nine viewpoints included: *strength of association, temporality, consistency, theoretical plausibility, coherence, dose-response relationship, experimental evidence, analogy, and specificity in causation*. This article is often quoted as the 'Bradford Hill criteria' and used to support causation when an association is observed. His long time colleague, Richard Doll [4] and others [5] have said these 'criteria' were in no way meant as a checklist for causation, but that is exactly how they are applied in many epidemiologic studies. Phillips and Goodman [6] emphasize that points unappreciated in the pioneering paper by Hill are (a) statistical significance is often taken inappropriately as evidence of causation

when an association is evaluated, (b) even if a strong association is observed, other evidence is required to support causation, and (c) no matter how precisely a study is conducted, bias cannot be totally eliminated. Considering the aforementioned admonitions, the nine viewpoints articulated by Hill can be used as a framework to evaluate the research performed by Ismail et al. [1]. We ascertain whether their hypothesis is more or less plausible.

Based on information provided in the paper by Ismail et al. [1], it is difficult to determine the *strength of association* between a change in milk processing and emergence of neonatal GBS disease. This is particularly true when other concurrent events are considered in causation. Although the timeline is rather short in the number of years, the change in milk transport does come before the increase in neonatal GBS infections in the UK. Thus, a most important criterion among Hill's viewpoints, namely *temporality*, is fulfilled. The association between neonatal GBS disease and a change in milk processing should have *consistency* among different populations. In the USA, bulk transport of milk from dairy farms to the processing plant began before 1920 and was widely established by 1940 [7]. Thus, bulk transport of milk to the processing plant occurred at least two decades before the emergence of the neonatal GBS epidemic in the USA. This observation suggests alternative associations may be

Table 1. Discovery of antibiotics and emergence of neonatal GBS disease

	Antibiotic production and use ^a				
	prontosil sulfonamide	penicillin	streptomycin aminoglycosides	tetracyclines aureomycin/terramycin	
Year	1935	1942	1943	1945	1950
Investigators	Domagk	Florey and Chain	Waksman	Duggar	Woodward
Major reports on neonatal GBS infections ^b					
Year	1961	1964	1967	1970	1973
Authors	Hood	Eickhoff	Butter and de Moor	Rogers	Baker
					Franciosi

^a URL source for antibiotic discovery, use and resistance: <http://www.textbookofbacteriology.net/>.

^b Harper [17] and McCracken [18] discuss the onset of the neonatal GBS epidemic.

operative in causation. The rational and theoretical basis for an association between a change in the UK between milk transport and the onset of increased neonatal GBS disease is incompletely discussed in the paper by Ismail et al. A *theoretically plausible* explanation is not offered on how a change in milk processing might have increased microbial pathogenesis related to the neonatal GBS epidemic. *Coherence* says there are no conflicts between the association and disease onset, and there are no plausible competing theories or rival hypotheses. Other hypotheses have been postulated for the neonatal GBS epidemic. Changes in diet, population mobility, social transformations, increased sexual promiscuity, enhanced microbiologic identification of GBS, better recognition of GBS as a cause of death, the influence of intrapartum antibiotics on GBS carriage by pregnant women, and other alterations in obstetrical care are among competing theories of causation [8–10]. Most of these associations have not had a strong causal inference or they have been refuted. This epidemiologic study discussed in this commentary is non-experimental and thus neither *dose-response relationships* nor *experimental evidence* allows the investigators to make an inference about causation. *Analogy* refers to applicability of a phenomenon already accepted in another area of investigation. An *analogy* is not available to support a causal association between UK-related changes in milk transport and the increase in neonatal GBS disease. Finally, *specificity in cause* predicts that one primary factor, such as a change in milk transport, has credibility as a claim for causation. As mentioned above, many explanations for the emergence of the neonatal GBS epidemic have been proposed [8–11]. Studies have also investigated genetic changes in *Streptococcus agalactiae* that

would increase its fitness to colonize pregnant women and thus allow transmission to the fetus [12–14]. These reports suggest alterations in milk transport from dairy farms are an improbable primary factor in causation.

Misuse of antibiotics can also be proposed as a plausible alternative cause for the rapid increase in neonatal GBS disease during the 1960s and 1970s. In human pregnancy, the reservoir for GBS is the distal intestine [15]. This is the reason why rectovaginal swabs are recommended to identify colonization with GBS during pregnancy [16]. The colonization of the urinary and vaginal tracts by *S. agalactiae* is a consequence of the rectal reservoir that harbors this bacterium during pregnancy [15]. One might envision that there is a temporal association between the advent of antibiotic use and an increase in rectal colonization by GBS during pregnancy (table 1). With the exception of penicillin, *S. agalactiae* rapidly developed high antimicrobial resistance to aminoglycosides, tetracyclines, and sulfonamides during the years that the neonatal GBS epidemic appeared [19]. Whether GBS-related rectal colonization was facilitated by its resistance to broad-spectrum antibiotics that ordinarily kill enteric bacteria is unknown. However, GBS resistance to environmental and therapeutic antimicrobials is likely to promote overgrowth. Further, the ability of the complex indigenous bacterial flora to exclude GBS may well be diminished by antimicrobials. Each of these possibilities has a well-established analogy in the pathogenesis of *Clostridium difficile* enterocolitis [20]. Moreover, the discovery of antibiotics, the increasing human therapeutic and agricultural utilization of antibiotics, and the development of antimicrobial resistance patterns by GBS, all fit the timeline of the emerging neonatal GBS epidemic. In addition to this *temporal* relationship,

the association has *strength* and *plausibility*. Reports that methicillin resistance increased pathogenic strains of *Staphylococcus aureus*, as well as *C. difficile*, in hospitals and communities adds an *analogy* to antibiotic use, the resistance of GBS to broad-spectrum antibiotics, and the emergence of neonatal GBS disease.

What about the assumption that a change in milk transport is evidence that serotypes associated with human GBS infections have arisen from a bovine GBS ancestor? Recent reports [14, 21] using molecular analysis of human and bovine GBS have concluded that a recent common ancestor may have been transferred from cattle to man; however, no ancestral strain of *S. agalactiae* has ever been identified in an infected human neonate. A search of PubMed and the Internet identifies no evidence that neonatal GBS disease is zoonotic in origin (search terms used: pregnancy, dairy cattle, neonatal infection and group B streptococci). This search revealed no evidence showing bovine GBS strains infected human neonates in the 1970s [8]. Manning et al. [22] proved that close contact to dairy herds can result in an occasional transmission of colonizing bovine genotypes from cattle to man via fecal shedding or contact with contaminated

milk. There were no GBS-related neonatal infections reported in this paper. The term ‘contaminated milk’ used by Manning suggests consumption of raw cow’s milk. By 1917, laws mandating sterilization of bovine milk in large US cities had been enacted [6]. GBS rarely survives pasteurization [23], and there is no evidence that transported milk that has been properly pasteurized before public consumption leads to human colonic colonization.

In conclusion, Ismail et al. present provocative research that associates a change in milk transport in the UK with the emergence of neonatal GBS disease. This adds an additional proposal to a number of attractive and existing hypotheses. Hopefully the paper will stimulate additional discussion by epidemiologists, microbiologists, infectious disease experts, and neonatologists about the origins of the neonatal GBS epidemic in Europe, Canada, and the USA.

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