ABSTRACT

Breastfeeding provides defense against infectious disease during early life. The mechanisms underlying this protection are complex but likely include the vast array of immune cells and components, such as immunoglobulins, in milk. Simply characterizing the concentrations of these bioactives, however, provides only limited information regarding their potential relationships with disease risk in the recipient infant. Rather, understanding pathogen and antigen specificity profiles of milk-borne immunoglobulins might lead to a more complete understanding of how maternal immunity impacts infant health and wellbeing. Milk produced by women living in 11 geographically dispersed populations was applied to a protein microarray containing antigens from 16 pathogens, including diarrheagenic *E. coli*, *Shigella* spp., *Salmonella enterica* serovar Typhi, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis* and other pathogens of global health concern, and specific IgA and IgG binding was measured. Our analysis identified novel disease-specific antigen responses and suggests that some IgA and IgG responses vary substantially within and among populations. Patterns of antibody reactivity analyzed by principal component analysis and differential reactivity analysis were associated with either lower-to-middle-income countries (LMICs) or high-income countries (HICs). Antibody levels were generally higher in LMICs than HICs, particularly for *Shigella* and diarrheagenic *E. coli* antigens, although sets of *S. aureus*, *S. pneumoniae*, and some *M. tuberculosis* antigens were more reactive in HICs. Differential responses were typically specific to canonical immunodominant antigens, but a set of nondifferential but highly reactive antibodies were specific to antigens possibly universally recognized by antibodies in human milk. This approach provides a promising means to understand how breastfeeding and human milk protect (or do not protect) infants from environmentally relevant pathogens. Furthermore, this approach might lead to interventions to boost population-specific immunity in at-risk breastfeeding mothers and their infants.