

The role of breastfeeding in childhood otitis media

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Abstract

Purpose of Review: To summarize the recent literature, both systematic reviews and recently published original studies not included within those reviews, on the relationship between breastfeeding and childhood otitis media (OM).

Recent Findings: There is clear evidence that breastfeeding is associated with a reduced risk of OM in childhood with sound biological plausibility to support that the association is likely causal. Any breastfeeding reduces OM risk in early childhood by 40-50%. Systematic reviews also support a further reduced risk for continued breastfeeding. Recent studies have estimated burden of disease savings if breastfeeding within countries and globally approached WHO guidelines. Cost savings per year for reduced cases of OM by increasing ever and exclusive breastfeeding rates are estimated to be millions of pounds or dollars for UK and Mexico.

Summary: Breastfeeding reduces OM in children. The burden of disease and economic impact of increasing breastfeeding rates and duration would be substantial.

Key Words: Breastfeeding and otitis; otitis media; breastfeeding rates; AOM; breast milk

Abstract:150 words

Body:2582 words

Introduction:

Burden of Otitis Media:

Acute Otitis Media (AOM) is usually caused by either a viral or bacterial pathogen and often treated with antibiotics. Young children are particularly at risk due to limited space in the middle ear and poor drainage from relatively tortuous Eustachian tubes. AOM is often accompanied by significant pain along with fever, acute loss of hearing, and general unwellness. AOM has a number of potential complications. Many AOM-prone children suffer from recurrent episodes in infancy and early childhood. Commonly, on resolution of the acute infection, there is a persistent middle ear effusion (otitis media with effusion-OME) with accompanying hearing impairment. OME can persist, causing longer term hearing impairment and interfering with language development, school performance and behaviour. AOM may result in perforation of the ear drum with chronic discharge (chronic suppurative otitis media). Less common complications include mastoiditis, brain abscess and meningitis.

Globally, there are an estimated 709 million cases of acute otitis media per year, an incidence of 10.85% (1). The peak incidence is in the 1-4-year age group (60.99%) although rates vary from 3.64% in Central Europe to 43.36% in Sub-Saharan Africa (1). The disease burden attributed to AOM in both established and emerging nations is considerable. It is the most common reason for prescription antibiotics in developed countries where AOM is estimated to affect more than 60% of children under one year and more than 80% of children under three years (2-4). There is also a considerable health burden from the sequelae of AOM. It is estimated that there are globally around 31 million cases of chronic suppurative otitis media, and the prevalence rate for AOM induced permanent hearing impairment is 30.82 per 10,000 (1). Furthermore, complications of AOM are estimated to cause the deaths of 21,000 people annually, with mortality rates being highest in the 0-5 year age group (1).

Although updated clinical guidelines have reduced the reliance on antibiotic therapy for mild, early, uncomplicated AOM (5), it is still the most common reason for antibiotic use in many countries (6). Apart from the associated health care burden, this widespread use of antibiotics increases the risk of community antibiotic resistance.

Given the high health care burden, a number of risk factors for AOM have been investigated. The factors currently identified for risk reduction are breastfeeding, avoidance of in utero and childhood passive tobacco smoke exposure, and avoidance of indoor air pollution (1). A recent Lancet mega-review that summarized the evidence on breastfeeding and maternal and child health outcomes from 28 individual systematic reviews, found breastfeeding has many health benefits for both

mothers and children(7). The Lancet findings also confirm the vital role that breastfeeding plays in the prevention of common childhood infectious diseases including AOM.

Breastfeeding and Otitis Media:

Human breast milk is tailor-made for infants (8). Breast milk delivers appropriate nutrition for each infantile developmental stage, and is packed with immune substances that may: directly influence microbial colonization with favourable bacteria; protect against colonization and infection by harmful bacteria and; influence immune programming (9). The WHO recommends exclusive breastfeeding up to the age of 6 months with continued breastfeeding for 2 years and beyond. Despite these recommendations, breastfeeding rates in many countries, especially high-income countries, are poor with rates of only 20% at 12 months (7). Additionally, in children under the age of 6 months, 63%, 61% and 55% are not exclusively breastfed in upper-middle income countries, low-middle income countries and low income countries respectively (7).

Almost all the recent literature outlining the links between breastfeeding and OM supports a reduced risk of OM associated with breastfeeding. Since 2013 there have been two systematic reviews, a non-systematic review and four original studies on this subject.

Data Syntheses: Systematic and non-systematic reviews (Table 1)

There have been three reviews published on the impact of BF on OM over the last 4 years

The most recent data synthesis on this topic is our groups 2015 systematic review and meta-analysis by Bowatte et al. (10), commissioned by the World Health Organization as part of the Mega-review recently published in the Lancet (11). Pubmed, Cinahl and Embase databases were searched from inception yielding 24 studies (18 cohorts and 6 cross-sectional). Overall, we found a 43% reduction of the risk of ever having AOM in the first 2 years of life but no reduced risk after the age of 2. In this systematic review, meta-analyses were possible only for particular exposure categories. Infants exclusively breastfed for 6 months compared with those not breastfed or breastfed for periods less than 6 months had a reduced risk of AOM up to the age of 2 years after pooling the ORs of 5 cohort studies (OR 0.57; 95%CI 0.44-0.75). We also found a risk reduction when comparing ever versus never breastfed infants: OR 0.67; 0.56-0.80 (5 studies). An additional meta-analysis was performed on 12 cohort studies in a more versus less exposure grouping. This category included ORs from all studies which compared a greater exposure of breastfeeding (more) to less breastfeeding. The meta-analysis also found a reduced risk of AOM up to 2 years: OR 0.76; 0.67-0.56.

A systematic review by Hornell et al. reviewed the literature published between January 2000 and June 2011 (12). They identified four publications on AOM; two systematic review/meta-analysis (13, 14) and two prospective cohorts (15, 16). After reviewing these publications without performing an overall pooled estimate, the authors concluded that there was convincing evidence of a protective dose and duration of breastfeeding on OM. The publications included in the Hornell et al. systematic review are described in the following sentences. The included systematic review by Ip et al. (13) found a pooled adjusted Odds Ratio from 5 cohort studies for the risk of AOM associated with any breastfeeding of 0.77; 95% CI 0.64-0.91 when compared with never breastfed infants. Additionally, Ip et al. found some evidence that longer duration of breastfeeding may confer greater protection; the pooled estimate for the risk of AOM associated with 3-6 months exclusive breastfeeding versus

never breastfed was: OR 0.5; 0.36, 0.70. The other included systematic review by Kramer and Kakuma (14) analysed two prospective cohorts with a total of 3762 children finding an increased risk of one or more episode of otitis media in the first 12 months (Risk Ratio 1.28;95%CI 1.04-1.57). One of the two additional cohort studies included in the Hornell et al. systematic review (birth cohort n = 1764) found a non-significant association between distinct lengths of breastfeeding exposure (<1mo, 1-3mo, 4+mo, 4-6mo, 7-11 mo, 12+mo), and prevalence of ear infections in either the first or second 6 months of life. Their findings may have been limited by lack of power in each of the exposure categories. The remaining cohort study on 926 children found that infants exclusively breastfed for six months had fewer infections than partially breastfed or never breastfed children (OR 0.37; 0.13, 1.05).

There was a large amount of overlap between the systematic reviews of Bowatte and Hornell with the Bowatte review including all but studies identified by Hornell along with an additional 15 studies.

A 2013 non-systematic review performed by the American Academy of Pediatric Dentistry, Chicago as an update on the effects of breastfeeding for dental professionals also found that breastfeeding was associated with a reduced risk of OM(17).

Original articles since 2013 (Table 2)

There have been 4 original research articles published since 2013 (18-21). Due to dates of publication (two studies(18, 20)) and inclusion/exclusion criteria (two studies on selected populations)(19, 21), none were included in either of the systematic reviews mentioned above; however, it is unlikely that their inclusion would have affected the direction of associations found as three of these articles found an association between breastfeeding and a reduced risk of AOM.

Most recently, Martines et al.(20) performed a case-control study on Sicilian children (204 cases with 204 age and sex matched controls). They found that children who were breastfed were much less likely to develop AOM or Otitis Media with Effusion (OME) following an upper respiratory tract infection (URTI) than those who had never been breastfed ; OR 0.5;95%CI 0.3-0.77.(20)

Ajetunmobi et al. (18) investigated 502,958 children in a retrospective population based Scottish cohort using linkage of birth, death, maternity, infant health, child health surveillance and admission records. They included all single births in Scotland between 1997 and 2009, following the children until March 2012. Based on information collected about feeding at the 6-8 week visit, infants were classified as either: exclusively breastfed, exclusively formula fed, or mixed feeding. Compared with exclusively breastfed children, there was an increased risk of hospitalization for AOM in the first 6 months of life for infants who were exclusively formula fed (Hazard Rate (HR) 2.13; 95%CI 1.26-3.59). This estimate was made following adjustment for a range of socio-economic factors. There was also an increased point estimate for those both breast and formula fed (mixed feeding) compared with exclusive breastfeeding but the 95% confidence interval included 1 (HR 1.5; 0.65-3.48). They also found increased risk of hospitalization within the first year of life for formula fed infants for a large range of illness including: infections (gastrointestinal, upper and lower respiratory tract, urinary, and non-specific fever); asthma; diabetes and dental caries. These increased risks persisted after stratification by area deprivation. There was no increased risk of hospitalization for AOM after the first 6 months of life. The lack of association after the age of 6 months is perhaps expected considering that AOM is usually treated in the community and it is also remarkable that an

association was found up to the age of 6 months. The huge population based sample along with the objective ascertainment of prospectively collected exposure and outcome data, contribute to the robustness and importance of this work.

Jenson et al. (19) investigated a population based cohort of 223 Inuit mother-child pairs in two towns on the west coast of Greenland (1999-2007). The primary purpose of this research was to assess the relationship between maternal organochloride exposure and OM in their children. The children were followed up at the age of 4-10 years. They classified breastfeeding status at 6 months as full, partial or not and did not find an association with breastfeeding although point estimates were below 1 suggesting protection for full or partially breastfed children. It may be that there was little power to detect an association given the number of participants.

The final article by Salah et al. was a retrospective hospital based cohort of 340 children. In a group of children aged less than 2 years attending an outpatient clinic for recurrent AOM (3 or more episodes in 6 months), factors were analysed which predicted further recurrence and treatment failure. They found that breastfeeding duration of less than three months (compared with more than three months) was associated with a significant chance of further recurrence and with treatment failure (failure of antibiotic treatment).

Mechanisms for the protective link between breastfeeding and AOM

Previously it was believed that the protective effect of AOM on breastfeeding was largely mechanical; the suction pressure required and positioning for breast feeding were thought to be advantageous for draining the Eustachian tubes in young infants, thereby preventing AOM. Another slightly older theory that may underlie the reduction in infectious disease enjoyed by breastfed babies is related to the immunomodulatory substances contained in breast milk. This theory has currently been re-invigorated through the recent interest in the human and more specifically the infant gut microbiome. It is now believed a specific symbiotic microbiome which is established early in life and, amongst other functions, is believed to protect the infant against pathogenic infections (22).

Breast milk is known to contain the building blocks for establishment of this microbiome in the form of human milk oligosaccharides (HMOs) along with a distinct breast milk microbiota. HMOs are indigestible sugars most prominent in the colostrum. The milk oligosaccharides from primates are unique in the mammalian kingdom in terms of their diversity and high percentage of fucosylation (23). There are over 200 different types of human HMOs (24) and 50-80% of these are fucosylated depending on the genetic makeup of the mother (25). They feature prominently in the colostrum (20-25g/L) and taper off in overall percentage for mature breast milk (5-20g/L) (26). Although these HMOs do not provide a source of energy for the infant, their unique branching and diversity makes them a perfect substrate for particular strains of bacteria that are known to be beneficial colonizers of the newborn.

Although there is a growing literature on the establishment of the infant gut microbiome and its importance for protection from gastrointestinal morbidity along with its capacity to correctly educate the infants immature immune system, less is known about the microbiome of the nasopharynx and its potential effect on protection from AOM. Recently, Biesbroek et al (27) investigated the nasopharyngeal microbiome in 101 exclusively breastfed and 101 exclusively formula fed infants.

They discovered a distinctly different bacterial community composition in the nasopharynx between the two feeding modes; with breastfed children having increased representation of *Dolosigranulum* and *Corynebacterium Sp.* and reduced representation of *Staphylococcus*, *Prevotella* and *Veillonella sp.* at 6 weeks of age.

Literature concerning cost savings from reduced AOM linked to increased breastfeeding

Given the convincingly positive findings for breastfeeding in relation to OM, some of the recent literature has focussed on reductions in OM and cost savings which could be achieved through greater uptake and continuation of breastfeeding. Pokhrel et al. (28) assessed the potential economic impact, from the point of view of the National Health Service, from improving breastfeeding rates in the U.K. Breastfeeding rates in the UK are comparatively low internationally with only 55% of infants breastfed at 6 weeks and only 23% exclusively (2010). They assessed the economic impact in terms of 4 acute childhood conditions in the first year of life: gastrointestinal illness, lower respiratory tract infections, AOM and necrotising enterocolitis, finding that for women who have initiated breastfeeding for the first week, an increase in breastfeeding duration up to 4 months would save 11 million pounds per year. For AOM these costs were based solely on the costs of treating AOM in primary care and did not appear to take into account the cost of complications, hospitalizations or the costs for parents who would need time off work to care for their children. Specifically, for AOM the cost saving was estimated to be between 0.28 and 1.16 million pounds per year depending on whether exclusive breastfeeding rates at 6 months increased to 21% OR 65% respectively. McIsaac et al. (29) studied potential reductions in common childhood infections in Aboriginal Canadians where AOM reduction may be arguably greater due to the increased prevalence of severe AOM in this population and relative decrease in breastfeeding when compared with general Canadian infants. They found a 5.1% to 10.6% reduction in OM in Aboriginal infants if they received any breastfeeding. The preventable proportion of infectious disease in Aboriginal infants was 1.5-2 times greater than the non-Aboriginal Canadian infants. Arantxa Colchero et al. (30) investigated the costs of inadequate breastfeeding in Mexican infants who experience very low rates of exclusive breastfeeding at 6 months; only 14% in 2012. They found if exclusive breastfeeding rates increased to 95% at 6 months and 95% partial breastfeeding between 6 and 12 months, then the savings related to reduced AOM could be between 0.5 and 15.4 million US dollars per year. This estimate increased when the cost of infant formula is added: 289.9 million dollars per year. Furthermore, the economic modelling from the Lancet mega-review using the Lives Saved Tool to estimate global impacts of increasing exclusive breastfeeding for 95% of all children at 1 month, and 90% at 6 months with partial breastfeeding of 90% between 6 and 23 months found a possible prevention of 823,000 deaths in children under the age of 5. This was largely from prevention of infectious disease in low-income countries (11).

Conclusions:

There appears to be little doubt that breastfeeding is beneficial for protecting infants from a range of infectious diseases including AOM. In addition, there are a number of other economic and health related reasons for promotion of breastfeeding in line with the WHO guidelines. Governments globally should promote and support breastfeeding through campaigns and measures designed to educate and support mothers, families and communities.

Compliance with Ethics Guidelines

Conflict of Interest

Drs. Lodge, Bowatte, Matheson, and Dharmage declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Table 1. Reviews of Breastfeeding and otitis media in past 4 years					
Authors & Date & Country	Study Type & inclusion criteria	Population & numbers	Exposure & how ascertained	Outcome & how Ascertained	Measured effect
Hornell et al 2013	<p>Systematic review</p> <p>Short and long term effects of breastfeeding and introduction to solids</p> <p>Inclusion Published since January 2000, human subjects Search date June 2011 English or Nordic language Nordic study population Exclusion Pro/pre biotics, special formulas eg supplemented (LC-PUFA), breast milk contamination, sick or high risk mothers and children, If only definition ever vs never</p>	<p>Population Nordic countries Number 60 quality assessed papers 13 SLR/MA; 41 prospective cohort; 6 from PROBIT trial; 13 reports</p> <p>4 of these on AOM – 2 prospective cohorts and 2 SLR/MA</p>	Duration of both any and exclusive breastfeeding Introduction of foods other than breast milk	<p>Grade of evidence ; convincing/probable/limited-suggestive/limited-no conclusion</p> <p>Quality Assessment Tols(QAT) from the NNR5 secretariat-included modified AMSTAR</p> <p>1p SLR (grade A) 5 cohort studies BF signif reduction in AOM</p> <p>Pooled adjusted OR s: ever vs never BF 0.77 (95%CI: 0.64, 0.91) Ex BF 3 - 6months vs never: 0.50 (0.36, 0.70)</p> <p>Prospective cohort studies: Fisk et al – birth cohort 1764 7 durations of breastfeeding (<1mo, 1-3mo, 4+mo, 4-6mo, 7-11 mo, 12+mo) – ear infections 0-6mo and 6-12 months. Non significant association bw Bf duration and prev of ear infections 0-6 and 6-12 months Ladomenou et al Ex bf for 6 months, fewer infections</p>	<p>Convincing evidence of a protective dose/duration effect of breastfeeding on acute otitis media</p> <p>Recommend unchanged nnr 2004 exclusive breastfeeding 6 months and continued partial breastfeeding thereafter</p>

				than partially and nonBF- adj OR 0.37 (0.13, 1.05)	
Bowatte et al 2015	Systematic Review and Meta-analysis Exclusion OME Non-english	Population 24 studies (USA or Europe) 18 cohort 6 cross-sectional Number	Ever versus never breastfeeding More versus less breastfeeding Exclusive BF for 6 months versus	Childhood Hospitalization for AOM until March 2012 (Follow-up period varied between 2.25 years and 15 years) Ascertainment Linkage of birth, death, maternity, infant health, child health surveillance and admission records	Reduced risk AOM in first 2 years of life (not after 2) Ex BF 6 months – 43% reduction in ever AOM in first 2 years EX BF 6 months vs other OR 0.57; 0.44-0.75 (5 cohorts) More vs Less BF Or 0.67 ;0.59, 0.76 (12 cohorts) Ever vs Never BF or 0.67 ;0.56, 0.80 (5 studies)
Salone et al 2013	A narrative review: studies published from January 1999 - March 2011	Includes: peer reviewed articles, systematic review and meta-analyses, and reports from major nongovernmental and governmental organizations	Not given: OM is a small part of health outcomes assessed	Not given	Compared with formula-fed children, the health advantages associated with breastfeeding include a lower risk of acute otitis media

Authors & Date & Country	Study Type & inclusion criteria	Population & numbers	Exposure & how ascertained	Outcome & how Ascertained	Measured effect
Martines et al 2016 Sicily	Case-Control Inclusion Children attending ED in Palermo with URTI then having OM diagnosed (either Acute otitis media-AOM or Otitis media with effusion EOM) within 21 days and age/sex matched controls	Population Sicilian children, Palermo Sep 2012 – June 2013 Number 204 children(106 males and 98 females) 204 age and sex matched healthy children	Breastfeeding ever Yes vs No Ascertainment Questionnaire (recall)	Current AOM or EOM ENT specialist on history and otoscopy Ascertainment Questionnaire (recall)	Risk of OM <u>breastfed vs non-breastfed</u> Chi square – 10.16 95% (p=0.0014) OR 0.5 CI (0.3, 0.77) This appears to be an unadjusted estimate
Ajetunmobi et al 2015 Scotland	Retrospective population –based Birth Cohort Exclusion Congenital anomalies, non-Scottish residents	Population Single births in Scotland 1997-2009 Number 502,948	Infant feeding at 6-8week age review <ol style="list-style-type: none">1. Exclusive breastfeeding2. Formula feeding3. Mixed breast and formula feeding Ascertainment	Childhood Hospitalization for AOM until March 2012 (Follow-up period varied between 2.25 years and 15 years) Ascertainment Linkage of birth, death, maternity, infant health, child health surveillance and admission records	Risk of hospitalization for OM Compared with exclusive breastfeeding (baseline) All ages: Mixed fed HR 1.04 (0.95- 1.14) Formula fed HR 1.03 (0.97- 1.09) ≤6months Mixed fed HR 1.5(0.65-3.48) Formula fed HR 2.13 (1.26- 3.59)

			Linkage of birth, death, maternity, infant health, child health surveillance and admission records		Adjusted for parental factors, delivery and infant health characteristics, features of health care system – exact variables unclear and deprivation area index, maternal ethnic and religious background
Jenson et al 2013 Greenland	Population based cohort (primary aim to assess the effects of organochloride exposure in mothers on otitis media in their children)	Population 400 mother –child pairs(400 pregnant women aged 16-46) living in three towns on west coast of Greenland (Nuuk, Ilulissat, Mantsiq) 1999-2007 Number limited to 251 children living in Nuuk and Ilulissat and 223 (85%) of these children followed up at 4-10 years	Breastfeeding status at 6 months 1. Full 2. Partly 3. No Ascertainment Mothers interviewed at 6 months	OM Ascertainment Ear examinations with tympanometry and gradings: 1. Chronic otorrhea (>14 days) 2. Chronic perforation (>3months) 3. Circular atrophy 4. Myringosclerosis 5. Diffuse atrophy 6. Retraction 7. Fibrosis 8. Unknown (ear wax obstructing view/uncooperative) 9. Normal OM history Ascertainment medical records	Risk of OM in first 4 years of life compared with no breastfeeding at 6 months Full breastfeeding: HR 0.85 (0.47-1.54) Partly breastfeeding HR 0.90 (0.54-1.49) Estimates adjusted for sex, ethnicity, mothers history of OM, mothers history of smoking
Salah et al.	Retrospective	Population	Breastfeeding	Recurrent AOM	Recurrent AOM

2013	<p>hospital-based cohort</p> <p>Exclusion Chronic otitis media with effusion, Typanostomy tube insertion</p>	<p>Recurrent AOM patients <2 years attending outpatient Pediatric Otolaryngology Unit, Cairo University Hospital (May 2011-April 2012)</p> <p>Number 340</p>	<p>duration > 3months versus < 3 months</p> <p>Ascertainment Review of hospital charts</p>	<p>(≥3 episodes in 6 months) at age 3-24 months Otoscopy – congested and/or bulging eardrum, or otorrhea and presence of acute signs of infection (fever, pain, irritability) Treatment failure Persistence or worsening of AOM for up to 1 week following initial treatment (antibiotics)</p>	<p>Unadjusted – Chi square 5.7 episodes of AOM (SD +-1.9) in infants breastfed < 3months cf 5.1 episodes AOM (SD 1.6) in infants breastfed > 3 months (p=0.005)</p> <p>Treatment failure Logistic regression(with unknown inclusion of other variables) showed that short breastfeeding (<3 months) was a “significant risk factor“ for treatment failure (p=0.006)</p>
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