Continuing Impact of Infectious Diseases on Childhood Deaths in England and Wales, 2003–2005

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Background: Data on the contribution of specific infections to childhood deaths in developed countries are limited.

Methods: Infection-related deaths in children aged 28 days to 14 years who died in England and Wales between 2003 and 2005 were identified from routine anonymized death certificate dataset provided by the Office for National Statistics to the Health Protection Agency, using predefined International Classification of Diseases codes for infection.

Results: There were 1368 infection-related deaths documented, constituting 20% of all childhood deaths. An underlying medical condition was recorded in 50% (676 cases), the most common being prematurity in infants (322/660, 52%), cerebral palsy in 1 to 4 year olds (46/190, 24%), and malignancy (46/163, 28%) in 5 to 14 year olds. Of the 837 deaths where a pathogen was coded, 494 (59%) specified bacterial infection, 256 (31%) viral infection, and 69 (8%) fungal infection. Among deaths with recorded bacterial infections, a lower proportion of meningococcal and pneumococcal infections (14% [22/155] vs. 60% [205/339], $P < 0.0001$) and a higher proportion of Gram-negative enteric bacilli (78/155 cases [50%] vs. 17/339 cases [5%], $P < 0.0001$) were reported in children with and without documented underlying medical conditions, respectively.

Conclusions: Infections continue to make a major contribution to deaths in children, particularly among those with underlying conditions. Identification of the pathogens associated with childhood deaths should help prioritize the development of intervention strategies for reducing pediatric mortality. Linkage of death registrations to national infectious disease surveillance systems should be undertaken to strengthen monitoring of infectious deaths and evaluate the effect of interventions.

Key Words: childhood mortality, infection, prevention, pathogens

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The United Kingdom has one of the highest mortality rates in children younger than 5 years (6.5/1000 live births) among Western European countries and the second highest among industrialized countries worldwide after the United States (8/1000 live births).[1] Infections are a significant and potentially preventable cause of death, particularly in young children.[2] However, most reported studies on infection-related deaths have focused on specific medical conditions or on single infections, with few population-based studies of all infection-related deaths in children. In the United Kingdom, the recent Confidential Enquiry into Maternal and Child Health (CEMACH, available at: www.cemach.org) reported infection to be the "largest single cause of death in children dying of an acute physical illness . . . despite comprehensive and expanding immunization programs, antibiotic availability, training in resuscitation, and life support."[3] The CEMACH report estimated that infection was relevant in at least 20% of the childhood deaths they reviewed, although the infections responsible were not discussed in detail.[3] Because completion of a death certificate by a clinician is a legal requirement in England and Wales, we used anonymized extracts of death registrations to determine the contribution of infections to childhood deaths in a 3-year period, with the aim of identifying key areas of priority for interventions to further reduce childhood mortality.

METHODS

In England and Wales, cause of death is classified according to the Tenth Revision of the International Classification of Diseases (ICD-10).[4] The Office for National Statistics (ONS) codes mortality data using software developed by the United States National Center for Health Statistics. The text within death certificates are converted to ICD-10 codes and computer algorithms apply selection and modification rules to assign the underlying cause of death. The Health Protection Agency routinely receives anonymized infectious disease-related death registration data from the ONS for public health surveillance purposes. Infection-related deaths are identified through an automated search of anonymized death registrations in England and Wales using predefined ICD-10 codes for infection (A00-B99, G00-G09, I00-I02, J00-J22, L00-L08, O75.3, O85, O86, O98, P35-P39). For this study, all deaths with any of the predefined ICD-10 codes in children aged 28 days to 14 years inclusive in England and Wales between January 2003 and December 2005 were included for further analysis. The ICD-10 codes and the corresponding death certificate terms in the final dataset were manually scrutinized and any deaths not considered to be caused by infection (such as those with a clear alternative cause of death) were excluded. Children with no underlying medical condition recorded on the death certificate were considered to have been previously healthy.

Age-specific incidence was calculated by dividing total number of deaths and infection-related deaths over the 3-year study period in the different age-groups by the ONS midyear population estimates for England and Wales for 2003–2005 combined (available at: www.statistics.gov.uk). Continuous data that did not follow a normal distribution were described as medians with interquartile ranges and compared using the Mann-Whitney U test. Proportions were compared using the χ^2 test or Fisher exact test, as appropriate. Rate ratios were used to statistically compare differences in incidence rates between males and females during the 3-year study period.

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RESULTS

There were 6987 deaths in children aged 28 days to 14 years in England and Wales between 2003 and 2005. During the same period, 2691 death certificates were identified with ICD codes potentially indicating an infectious contribution to death. Of these, 1323 cases were excluded after manual scrutiny because the deaths either occurred in the neonatal period (<28 days) or were not considered infection-related. Thus, 1368 infection-related deaths were identified between 2003 and 2005, accounting for 19.8% (1368/6897) of all childhood deaths in England and Wales. The overall (240 vs. 200 per 100,000 population; rate ratio: 1.22; 95% CI: 1.16–1.28; $P < 0.0001$) and infection-related (47 vs. 40 per 100,000 population; rate ratio: 1.16; 95% CI: 1.05–1.30; $P = 0.005$) mortality rate was higher in boys than in girls, but the proportion of infection-related deaths among boys who died was similar to that in girls who died (753/3870 (19.5%) vs. 615/3027 (20.3%), $\chi^2(1\ df) = 0.79$, $P = 0.37$). Among infection-related deaths, the median age was 1 year (interquartile range, 0–3 years) and 55.0% (753/1368) were male. The contribution of infection to childhood deaths was highest in the 1 to 4 year age group (27.3% of all deaths), followed by <1 year olds (21.4%) and 5 to 14 year olds (12.3%) (Table 1). Infection-related deaths were higher in the winter months compared with the summer months for both children with and without underlying medical conditions (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A390). There were 11 HIV-related deaths that were analyzed separately.

Underlying Medical Conditions

An underlying medical condition was stated on the death certificate in half (676 cases, 49.8%) of the 1357 non-HIV infection-related deaths (Table 2). The proportion of children with an underlying medical condition was significantly higher in 5 to 14 year olds than <5 year olds (163/266 [61.3%] vs. 322/654 [47.0%], $\chi^2(1\ df) = 17.4$, $P < 0.0001$; Table 2). In the 28 day to 1 year group, prematurity and associated problems were the most common underlying condition (58.4%) (Table 2). Among 1 to 4 year olds, cerebral palsy (24.1%) was the most common underlying problem, whereas malignancy predominated in the 5 to 14 year age group (28.2%). The proportion of deaths in children with any form of an underlying immunologic deficit (excluding malignancy) increased with age, from 5.9% of <1 year olds to 10.5% of 1 to 4 year olds and 17.2% of 5 to 14 year olds. Girls who died were more likely to have an underlying medical condition than boys (328/610 [53.8%] vs. 48/747 [46.6%], $\chi^2(1\ df) = 6.93$, $P = 0.008$), although there were no significant differences in the prevalence or type of underlying conditions between boys and girls.

Focus of Infection

Septicemia was the most common infection-related clinical presentation stated on the death certificate (629/1357, 46.4%), followed by respiratory tract infections (409 cases, 30.1%) and infections of the central nervous system (219 cases, 16.1%). Children with

TABLE 1. The Contribution of Infection to Childhood Deaths in England and Wales, 2003–2005*

	28 Days–1 Year	1–4 Year	5–14 Year	28 Days–14 Year
All-cause death rates/100,000 population				
Male	860	240	120	240
Female	700	210	100	200
Both	780	220	110	220
Infection-related deaths/100,000 population				
Male	186	66	13	47
Female	148	55	14	40
Both	167	61	14	44
No. infection-related deaths				
Male	376	244	133	753
Female	284	193	138	615
Both	660	437	271	1368

Rates are per 100,000 population within the age group specified.

TABLE 2. Number (%) of Underlying Medical Conditions by Age-Group Among Infection-Related Childhood Deaths, England and Wales (2003–2005)

	28 Days–1 Year (n = 654)	1–4 Year (n = 437)	5–14 Year (n = 266)	All Ages (28 d–14 yr) (n = 1357)
Any underlying medical condition	322 (49.2)	191 (43.7)	163 (61.3)	676 (49.8)
Underlying medical condition				
Prematurity	188 (58.4)	2 (1.0)	0 —	190 (28.1)
Congenital heart disease	33 (10.2)	13 (6.8)	5 (3.1)	50 (7.4)
Multiple congenital abnormalities	2 (7.1)	5 (2.6)	1 (0.6)	29 (4.3)
Chromosomal disorder*	18 (5.6)	22 (11.5)	7 (4.3)	57 (8.4)
Neurological disorder	6 (1.9)	24 (12.6)	10 (6.1)	44 (6.5)
Cerebral palsy	7 (2.2)	46 (24.1)	33 (20.2)	86 (12.7)
Immune deficiency	19 (5.9)	20 (10.5)	28 (17.2)	67 (9.9)
Malignancy	1 (0.3)	31 (16.2)	46 (28.2)	78 (11.5)
Metabolic disorder	8 (2.5)	7 (3.7)	18 (11.0)	33 (4.9)
Other	17 (5.3)	23 (12.0)	18 (11.0)	58 (8.6)
Total	322 (100)	437 (100)	163 (100)	676 (100)

*Includes Down syndrome, Turner syndrome, Edwards syndrome, Patau syndrome, and other chromosomal disorders.

underlying medical conditions were more likely to have septicemia reported than children without underlying conditions (384/676 [56.8%] vs. 245/681 [36.0%], $\chi^2(1\ df) = 59.2$, $P < 0.0001$) across all age groups. Children with no underlying medical conditions were more likely to present with meningitis or encephalitis (175/681 [25.7%] vs. 44/676 [6.5%], $\chi^2(1\ df) = 92.3$, $P < 0.0001$). Clinical presentations among previously healthy children also varied with age, with respiratory tract infections (122/332 cases, 36.7%) being most prevalent in infants deaths (<1 year), septicemia (105/246 cases, 43.5%) in 1 to 4 year olds, and meningitis or encephalitis (39/103 cases, 37.9%) in 5 to 14 year olds.

Infectious Pathogens

Of the 1357 children infection-related deaths, 837 (61.7%) had at least one pathogen specified on their death certificate (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A391). Of these, 507 (60.6%) were bacteria (including 13 [1.6%] mycobacteria), 256 (30.6%) viruses, 69 (8.2%) fungi, and 5 (0.6%) other infections. The pathogen responsible was more likely to have been reported for deaths in previously healthy children (472/681 [69.3%] vs. 340/676 [50.3%], $\chi^2 = 51.0$, $P < 0.0001$).

Nonmycobacterial bacterial infections were reported in half of all infection-related deaths among previously healthy children compared with approximately one-quarter (339/681 [49.8%] vs. 155/676 [22.9%], $\chi^2(1\ df) = 106$, $P < 0.0001$) of those with underlying medical conditions, where the infectious agent was less likely to be specified (320/676 [47.3%] vs. 197/681 [28.9%], $\chi^2(1\ df) = 47.8$, $P < 0.0001$). Among bacterial infections, meningococci were the most commonly reported organisms (138 cases; 27.9%), followed by pneumococci (89 cases, 18.0%) and other streptococci (62 cases, 12.9%), including group B (25 cases, 5.1%) and group A (16 cases, 3.2%) streptococci. Deaths reported to be due to meningococcal infection were substantially more common in previously healthy children than those with underlying medical conditions (133/339 [39.2%] vs. 1/155 [3.2%], $\chi^2(1\ df) = 70.8$, $P < 0.0001$). All 9 pertussis-related deaths occurred in previously healthy infants younger than 4 months of age, of whom 6 were younger than 2 months. In children with underlying medical conditions, Gram-negative enteric bacilli accounted for greater than half of all bacterial infections (80/155 cases, 51.6%) compared with only 5.0% (17/339 cases) among previously healthy children ($\chi^2(1\ df) = 146$, $P < 0.0001$) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A391). Enterococcal and staphylococcal infections contributed a further 20% of deaths in children with underlying conditions where a pathogen was specified.

The proportion of infection-related deaths that mentioned a viral infection was similar in previously healthy children and those with underlying medical conditions (134/676 [19.8%] vs. 122/681 [17.9%], $\chi^2(1\ df) = 0.81$, $P = 0.37$). Over half the viral infections were caused by 4 viruses: respiratory syncytial virus (RSV) (16.4%), adenovirus (12.5%), influenza (11.7%), and cytomegalovirus (CMV) (10.5%) (Table, Supplemental Digital Content 2, http://links.lww.com/INF/A391). RSV was noted in greater than a quarter (34/134 cases, 25.4%) of viral deaths in children with underlying medical conditions compared with only 6.6% (8/122 cases) among previously healthy children ($\chi^2(1\ df) = 16.5$; $P < 0.0001$). All but 2 RSV-related deaths (40/42 cases, 95.2%) occurred in children <5 years and all 8 RSV-related deaths among previously healthy children occurred in infants. In children with underlying medical conditions, the proportion of deaths associated with adenovirus increased with age. Twenty-seven deaths in children revealed CMV infection as a contributing factor, including 17 with congenital infection (designated as previously healthy children in Table, Supplemental Digital Content 2, http://links.lww.com/INF/A391), as they had no identifiable underlying medical condition before developing CMV infection), most of whom (11/17 cases) died within the first year of life; 6 others died at an older age from a long-term complication of the congenital infection (eg, aspiration pneumonia).

Of the 11 HIV-related deaths, 6 were aged <1 year and the remaining 5 were 8 to 12 years. The reported causes of death were tuberculosis (3 cases), *Pneumocystis jiroveci* pneumonia (2 cases), RSV bronchiolitis (2 cases, both premature infants), and 1 case each of HIV encephalopathy, non-Hodgkin lymphoma, pneumonia (pathogen not specified), and septicemia (pathogen not specified).

Deaths specifying pathogens other than bacteria and viruses were rare (90/1357 cases, 6.6%), particularly among previously healthy children (23/681 [3.4%] vs. 67/676 [9.9%], $\chi^2(1\ df) = 23.4$, $P < 0.0001$). Of note, 9 of 13 mycobacterial deaths occurred in previously healthy children, with 6 occurring among 10 to 14 year olds. By contrast, deaths mentioning fungal pathogens were more prevalent in children with underlying medical conditions (5/681 [0.7%] vs. 64/676 [9.5%], $\chi^2(1\ df) = 51.8$, $P < 0.0001$). Two deaths in previously healthy children pointed out malaria and *Toxoplasma* infection (5–14 year age group) as contributory causes, and 2 further deaths in children with underlying medical conditions mentioned *Mycoplasma* and cysticercosis.

DISCUSSION

We have described, for the first time, the contribution of specific infections to childhood deaths in England and Wales. Infections contributed to at least one-fifth of all non-neonatal childhood deaths. An underlying medical condition was noted in half of the infection-related childhood deaths. Our estimates are comparable with the recent CEMACH pilot study,[3] but must be considered a minimum for several reasons. The information contained within death certificates is known to be limited and may be incomplete.[3,5–7] In some cases, an infection may not be stated on the death certificate when it clearly contributed to the death.[8] This may particularly be the case in children with multiple underlying medical problems where an infection was not considered to directly contribute to death.[9] In addition, certifiers may only state the clinical manifestation of the infection (eg, pneumonia or septicemia), may preferentially state specific organisms (eg, methicillin-resistant *Staphylococcus aureus* [MRSA]), or may not be aware that a pathogen had been identified at the time of completing the death certificate.[9] In a recent analysis of deaths within 7 days of invasive group A streptococcal infection, only 5 of 557 (9.0%) specifically mentioned group A streptococci on the death certificate.[10] The time between diagnosis and death may also play a part in the information provided on the death certificate. In a study of deaths after MRSA bacteremia, the pathogen was more likely to be stated on the death certificate if the death occurred at least 2 days after the diagnosis was made, whereas those who died within 2 days were more likely to have "unspecified septicemia" documented.[9] We also excluded all cases of sudden unexpected death in infancy, even though there is increasing evidence for the role of infection in its pathogenesis.[11,12]

The methodology used to identify infection-related deaths in our study also has its limitations. The text in the death certificates were manually assigned to the most appropriate ICD-10 codes, which may not always be accurate. Moreover, it is possible that the predefined ICD-10 codes used to extract infection-related deaths were not comprehensive enough and may, therefore, have missed some infection-related deaths. Finally, because of the limited information contained in death certificates, there was no way of determining the exact contribution of the infection to death.

Despite these limitations, we have established a minimum estimate for the contribution of infections to childhood deaths in England and Wales between 2003 and 2005. We have also attempted to describe the contribution of specific pathogens to

deaths in previously healthy children and those with underlying medical conditions. It was not possible to determine whether the excess childhood deaths in England and Wales compared with other Western European countries are caused by infections because similar data from other developed countries are lacking. However, infection-related deaths are potentially preventable and interventions targeted at prevention, rapid diagnosis, and improved clinical management of infections may have a significant effect on overall childhood mortality rates.

Infant immunization remains the most effective method of preventing serious infections in children and, consequently, infection-related sequelae, and death.[2] Expanding the immunization program as newer and/or more effective vaccines become available will continue to offer benefits. Currently available vaccines not included in the national infant immunization program that have the potential to further reduce childhood infections include the influenza,[13,14] hepatitis B,[15,16] rotavirus,[17–19] varicella,[20] and quadrivalent meningococcal conjugate[21,22] vaccines, while promising vaccines including the 13-valent pneumococcal conjugate vaccine,[23] meningococcal group B vaccine,[24] and the live-attenuated RSV vaccine,[25] have already entered clinical trials in humans.[26] Depending on vaccine uptake and efficacy, a meningococcal group B vaccine, for example, has the potential to prevent 46 childhood deaths a year.

In addition to primary immunization, infection-related deaths in children may be reduced through early recognition, improved diagnostic methods, and aggressive management of critically ill children. The CEMACH report recently identified that healthcare professionals in both primary care and hospital had difficulty in recognizing serious illness in children, and that there was a failure in implementing national guidelines.[3] The development of training, clinical decision-making tools, and clinical care pathways, therefore, could help to improve early recognition of life-threatening infections. In addition, the predominance of deaths caused by Gram-negative enteric bacilli in children with underlying medical problems is of concern particularly in the era of increasing antimicrobial resistance. Further studies are required to determine whether this group of children may benefit from antibiotics with increased activity against Gram-negative bacteria.

In conclusion, this is the first study to determine the overall burden of specific infections to childhood mortality in England and Wales. The organisms responsible for deaths in children with underlying medical conditions are different than those affecting previously healthy children. Our results also support the findings of the recent CEMACH report relating to infection-related deaths, which identified infection control, optimal antibiotic prescribing, and vigilance to be the key priorities in planning and delivering healthcare to children.[3] There is a clear need for an integrated approach to link laboratory, epidemiologic, prescribing, and clinical outcome data. To date, linkage studies in England and Wales have only been performed for specific infections, such as invasive group A streptococci and MRSA.[10,27] Broader linkage to include all infections would allow prospective monitoring of infection-related deaths in children and provide an evidence base to prioritize research and interventions to key areas of importance in reducing childhood mortality.

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