Mortality and its risk factors in Malawian children admitted to hospital with clinical pneumonia, 2001–12: a retrospective observational study

Marzia Lazzerini, Nadine Seward, Norman Lufesi, Rosina Banda, Sophie Sinyeka, Gibson Masache, Bejoy Nambiar, Charles Makwenda, Anthony Costello, Eric D McCollum, Tim Colbourn

Summary

Background Few studies have reported long-term data on mortality rates for children admitted to hospital with pneumonia in Africa. We examined trends in case fatality rates for all-cause clinical pneumonia and its risk factors in Malawian children between 2001 and 2012.

Methods Individual patient data for children (<5 years) with clinical pneumonia who were admitted to hospitals participating in Malawi's Child Lung Health Programme between 2001 and 2012 were recorded prospectively on a standardised medical form. We analysed trends in pneumonia mortality and children's clinical characteristics, and we estimated the association of risk factors with case fatality for children younger than 2 months, 2–11 months of age, and 12–59 months of age using separate multivariable mixed effects logistic regression models.

Findings Between November, 2012, and May, 2013, we retrospectively collected all available hard copies of yellow forms from 40 of 41 participating hospitals. We examined 113 154 pneumonia cases, 104 932 (92·7%) of whom had mortality data and 6903 of whom died, and calculated an overall case fatality rate of 6·6% (95% CI 6·4–6·7). The case fatality rate significantly decreased between 2001 (15·2% [13·4–17·1]) and 2012 (4·5% [4·1–4·9]; $p_{trend}<0·0001$). Univariable analyses indicated that the decrease in case fatality rate was consistent across most subgroups. In multivariable analyses, the risk factors significantly associated with increased odds of mortality were female sex, young age, very severe pneumonia, clinically suspected *Pneumocystis jirovecii* infection, moderate or severe underweight, severe acute malnutrition, disease duration of more than 21 days, and referral from a health centre. Increasing year between 2001 and 2012 and increasing age (in months) were associated with reduced odds of mortality. Fast breathing was associated with reduced odds of mortality in children 2–11 months of age. However, case fatality rate in 2012 remained high for children with very severe pneumonia (11·8%), severe undernutrition (15·4%), severe acute malnutrition (34·8%), and symptom duration of more than 21 days (9·0%).

Interpretation Pneumonia mortality and its risk factors have steadily improved in the past decade in Malawi; however, mortality remains high in specific subgroups. Improvements in hospital care may have reduced case fatality rates though a lack of sufficient data on quality of care indicators and the potential of socioeconomic and other improvements outside the hospital precludes adequate assessment of why case-fatality rates fell. Results from this study emphasise the importance of effective national systems for data collection. Further work combining this with data on trends in the incidence of pneumonia in the community are needed to estimate trends in the overall risk of mortality from pneumonia in children in Malawi.

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Introduction

Pneumonia is the leading cause of morbidity and mortality in post-neonatal children under 5 years of age.[1] According to the most recent estimates,[1] 0·9 million children died of pneumonia in 2013, and more than 95% of these deaths happened in low-income and middle-income countries.[1,2]

Few data are available to show the epidemiology and public health burden of paediatric pneumonia cases in African hospitals. A recent systematic review[3] identified only 11 studies reporting data on mortality from acute lower respiratory infections in hospitals within the African region; these reports were unpublished, with very few exceptions,[4] and observation times were limited to 2–3 years.[3]

Malawi is currently one of the poorest countries in sub-Saharan Africa. However, according to national statistics,[5] major progress was made in the past 15 years, and Malawi is on track to reach the Millennium Development Goal 4 of a two-thirds reduction in under-5 year mortality from 1990 to 2015.

In 2000, the Malawi Ministry of Health implemented a standardised medical chart for children younger than 5 years who were admitted to hospital with clinical

Research in context

Evidence before this study

A recent systematic review identified only 11 studies reporting data on mortality in children admitted to hospital with acute lower respiratory infections in the African region, and with very few exceptions, reports were unpublished, and with an observation time limited to 2–3 years. We also searched PubMed using the following search strategy: ("Pneumonia"[Mesh] OR "Respiratory Tract Infections"[Mesh]) AND ("Child"[Mesh] OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) OR ("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields]) OR ("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields])) AND ("Malawi"[MeSH Terms] OR "Malawi"[All Fields]) from inception to July 8, 2015, with no language restrictions. We found 68 studies, none of which covered the range of years and numbers of hospitals of our study.

Added value of this study

We have analysed an individual patient database of hospitalised cases of pneumonia in children in Malawi, collected over a 12 year period. The data shows a clear decline in case fatality rate between 2001 and 2012, although this rate remains high in some subgroups (children with very severe pneumonia, severe undernutrition, severe acute malnutrition, and symptom duration >21 days).

Implications of all the available evidence

Overall, our study supports the finding from the Millennium Development Goal 4 indicators that under-5 mortality has significantly decreased in Malawi in recent years. Further research is needed to link hospital data with community-based pneumonia data and to investigate quality of care provided to children at different levels of the health system.

Panel: Classification of severity of clinical pneumonia[10]

Non-severe pneumonia (2–59 months of age)*
- Cough, difficulty breathing, or both
- Fast breathing for age†
- No lower chest indrawing and no danger signs‡

Severe pneumonia (<2 months of age)
- Cough, difficulty breathing, or both, and
- Lower chest indrawing or fast breathing for age*†
- No danger signs‡

Severe pneumonia (2–59 months of age)
- Cough, difficulty breathing, or both
- Lower chest indrawing
- No danger signs‡
- Might or might not have fast breathing for age†

Very severe pneumonia (0–59 months of age)
- Cough, difficulty breathing, or both
- At least one danger sign‡
- Might or might not have fast breathing for age†
- Lower chest indrawing

*Young infants younger than 2 months do not have a non-severe pneumonia classification. †60 breaths per min or more if child is younger than 2 months; 50 breaths per min or more if child is 2–11 months old; 40 breaths per min or more if child is 12–59 months old. ‡Danger signs are any of the following: central cyanosis, severe respiratory distress (grunting, head nodding, severe chest indrawing), stridor, a general danger sign (inability to drink, breastfeed, or both, lethargy or unconsciousness, convulsions), apnoea (if child is 0–2 months of age). Wheeze is not considered in diagnosis or classification of severity of pneumonia.[10]

pneumonia. These data have been routinely collected prospectively but never comprehensively analysed. We have analysed the available individual patient data from hospitals in Malawi that implemented this routine system of data collection between 2001 and 2012, with the objective of describing trends in case fatality rates for all-cause clinical pneumonia and its risk factors in children younger than 5 years.

Methods

Study design and participants

In 2000, the Malawi Ministry of Health's Acute Respiratory Infection unit (ARI) and the International Union Against Tuberculosis and Lung Disease implemented the Child Lung Health Programme (CLHP),[6,7] which included two key elements: national clinical pneumonia management guidelines[8] adapted from WHO guidelines;[9,10] and the implementation of a standardised patient chart (the yellow form) to be used as an official medical file for each child admitted to hospital for pneumonia. CLHP clinical pneumonia was defined according to Malawi ARI guidelines (panel). The yellow form contains individual patient data such as demographic variables, clinical signs and symptoms, pneumonia disease severity, comorbidities, treatments received, and outcomes (appendix pp 3–4). The following criteria were used for CLHP programme participation: an active ARI programme; leadership commitment; one health worker responsible for implementation (local ARI coordinator); and about 100 000 population catchment area.[6] District government hospitals were prioritised for participation in CLHP, and by 2004, 22 of 23 district hospitals and three of four central government hospitals were enrolled.[6] In 2005, with the support of the Scottish Government, the programme expanded to include the Christian Hospital Association of Malawi hospitals, which are mostly first-level, fee-based facilities. By 2012, 22 of 23 district hospitals, three of four central hospitals, and 16 of 37 Christian Hospital Association of Malawi facilities were participating in the CLHP (appendix p 5).

From 2001 to 2005, major external support was provided to the CLHP: health staff were trained in the programme, which included a follow-up refresher session and on-the-job training; international expert technical guidance that focused on maintaining data quality, accuracy, and completeness was provided twice annually; and

See Online for appendix

programme managers met regularly to review their work.[6] The CLHP also provided an uninterrupted supply of antibiotic drugs for pneumonia treatment.[6] Between 2006 and 2008, the programme was gradually transitioned to the Ministry of Health, whereas external assistance focused on enrolling facilities from the Christian Hospital Association of Malawi using previous approaches. In 2009, the Ministry of Health assumed primary control and arranged supervision visits and follow-up trainings according to local needs and available funding.

Between November, 2012, and May, 2013, the study authors and data collectors employed by PACHI (the local research organisation conducting the study) collected all available hard copies of yellow forms from 40 of the 41 participating hospitals, where the forms were stored (usually under the supervision of the local ARI coordinator). Standardised data cleaning and data entry, including systematic quality assurance checks, were done by data entry clerks and nurses under close supervision by ML, RB, and SS. Confidentiality was maintained by de-identifying all files before database entry.

This study was approved by the Ethics Committee of University College London (project number 2006/002) and by the National Health Sciences Research Committee of Malawi (protocol number 941).

Descriptive and statistical analyses

Our descriptive analyses focused on the following outcomes: annual case fatality rates, annual case fatality rates in predefined population subgroups, and changes in children's characteristics with time. Young infants (defined as infants younger than 2 months) and children age 2–59 months were analysed separately since pneumonia classification and treatment differs in these two groups, according to WHO guidelines.[8–10] Weight-for-age was analysed according to WHO 2006 standards applied retrospectively to the dataset.[11] WHO moderate undernutrition and severe undernutrition were defined as weight-for-age ranging between –3 and –2 SD from the median and weight-for-age less than –3 SD from the median, respectively. The clinical diagnosis of severe acute malnutrition was made prospectively during patient care on the basis of visible signs of wasting or oedema of both feet as per Malawi guidelines.[8–10] Pneumonia and fast breathing were defined according to standard WHO criteria (panel). Fever was defined as body temperature greater than 38°C.

We compared mortality rates in patients for whom we had data on basic demographic variables and risk factor variables with rates in patients with missing data using the χ^2 statistic, Fisher's exact test, or *t* test, as appropriate, to informally investigate the likelihood that missing data could substantially bias subsequent analyses. We also did sensitivity analyses assuming different probabilities of mortality for the cases missing data on mortality relative to cases with data (0, 0·1x, 0·5x, 2x, 10x, and 1, where x is the probability of mortality in cases with data).

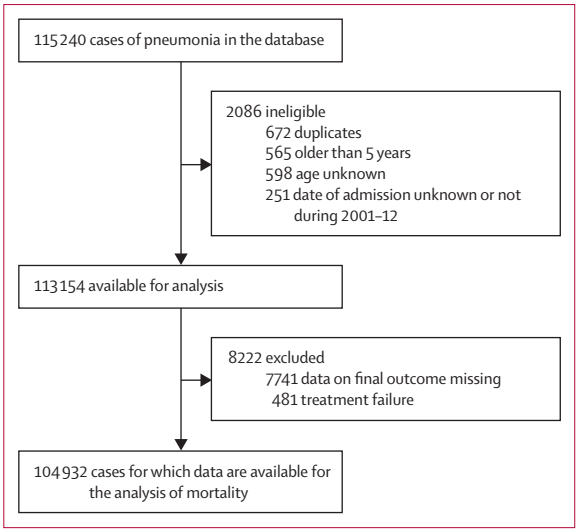

Figure 1: **Study flow diagram**

We compared rates by year using the χ^2 test for trend (Cochrane–Armitage test). Univariable logistic regression was used to calculate odds ratios (ORs) for mortality associated with each risk factor in each age group and in different population subgroups; survival time until death was not recorded (appendix p 3–4), precluding Cox regression.

For all statistical tests, a p value of 0·05 or less (two-sided) was considered significant. We used Stata version 13·1 for all analyses.[12]

Three multivariable logistic regression models were created to determine risk factors for mortality for pneumonia cases admitted to hospital in children younger than 2 months, age 2–11 months, and age 12–59 months separately. We used bootstrap resampling of stepwise backwards elimination with a p value cutoff greater than 0·05 for leaving the model to build multivariable models for each age group.[13,14] All variables except HIV and malaria (risk factors for which too much data were missing) were initially entered into each of 100 bootstrap replications, and variables that were selected in more than 50% of the replications were included in the final models.[13,14] As pneumonia cases were included from 40 hospitals, mortality could be correlated within hospitals. Likelihood ratio test confirmed the clustered nature of the data, and we used mixed effects logistic regression models to account for this. Results of the multivariable logistic regression analyses are presented as adjusted OR (AOR) with 95% CI. Events per variable[15] and area under the receiver-operator-characteristic (ROC) curve are presented as measures of model adequacy and goodness of fit.

To reduce bias and loss of information due to missing data, we used multiple imputation with the assumption that data was missing at random. Data showed evidence of clustering, so we used REALCOM impute software to impute missing data.[16] Variables in the multiple imputation models included the mortality outcome, risk

	Younger than 2 months (n=10 860)			2–59 months (n=102 294)			Total (%) n=113 154
	Survived (%) n=9247	Died (%) n=712	Missing (%) n=901	Survived (%) n=88 782	Died (%) n=6191	Missing (%) n=7321	
Region of Malawi							
Northern	1641 (18%)	128 (18%)	104 (12%)	16 914 (19%)	1059 (17%)	1101 (15%)	20 947 (19%)
Central	4098 (44%)	334 (65%)	480 (53%)	38 247 (43%)	2456 (40%)	3166 (43%)	48 781 (43%)
Southern	3508 (38%)	250 (35%)	316 (35%)	33 612 (38%)	2676 (43%)	3053 (42%)	43 415 (38%)
Missing	0	0	1 (<1%)	9 (<1%)	0	1 (<1%)	11 (<1%)
Type of facility							
District	7250 (78%)	556 (78%)	616 (68%)	71 089 (80%)	4993 (81%)	4710 (64%)	89 214 (79%)
Central	888 (10%)	79 (11%)	61 (7%)	7978 (9%)	554 (9%)	639 (9%)	10 199 (9%)
Mission or rural	1109 (12%)	77 (11%)	223 (25%)	9706 (11%)	644 (10%)	1971 (27%)	13 730 (12%)
Missing	0	0	1 (<1%)	9 (<1%)	0	1 (<1%)	11 (<1%)
Sex							
Female	3880 (42%)	303 (43%)	380 (42%)	38 858 (44%)	3097 (50%)	3933 (54%)	49 639 (44%)
Male	5109 (55%)	386 (54%)	475 (53%)	48 128 (54%)	2947 (48%)	3121 (43%)	60 978 (54%)
Missing	258 (3%)	23 (3%)	46 (5%)	1796 (2%)	147 (2%)	267 (4%)	2537 (2%)
Severity of pneumonia in children age 2–59 months							
Very severe	N/A	N/A	N/A	19 186 (22%)	3804 (61%)	1916 (26%)	24 906 (24%)
Severe	N/A	N/A	N/A	66 872 (75%)	2206 (36%)	4904 (67%)	73 982 (72%)
Non-severe	N/A	N/A	N/A	1581 (2%)	46 (1%)	273 (4%)	1900 (2%)
Pneumocystis jirovecii	N/A	N/A	N/A	169 (<1%)	74 (1%)	36 (1%)	279 (<1%)
Other	N/A	N/A	N/A	65 (<1%)	2 (<1%)	0	68 (<1%)
Missing	N/A	N/A	N/A	909 (1%)	58 (1%)	192 (3%)	1159 (1%)
Severity of pneumonia in infants <2 months							
Very severe	4082 (44%)	528 (74%)	338 (38%)	N/A	N/A	N/A	4948 (46%)
Severe	5010 (54%)	165 (23%)	506 (56%)	N/A	N/A	N/A	5681 (52%)
Pneumocystis jirovecii	15 (<1%)	3 (<1%)	5 (1%)	N/A	N/A	N/A	23 (<1%)
Other	3 (<1%)	0	0	N/A	N/A	N/A	3 (<1%)
Missing	137 (2%)	16 (2%)	52 (6%)	N/A	N/A	N/A	205 (2%)
Days with symptoms (before admission)							
<21 days	8234 (89%)	637 (90%)	781 (87%)	79 003 (89%)	5260 (85%)	6284 (86%)	100 199 (89%)
>21 days	167 (2%)	14 (2%)	17 (2%)	2284 (3%)	336 (5%)	255 (4%)	3073 (3%)
Missing	846 (9%)	61 (9%)	103 (11%)	7495 (8%)	595 (10%)	782 (11%)	9882 (9%)
Antibiotic treatment prior to hospital attendance							
No	4844 (52%)	359 (50%)	438 (49%)	43 805 (49%)	2534 (41%)	3213 (44%)	55 193 (49%)
Yes	2090 (23%)	175 (25%)	203 (23%)	23 040 (26%)	2080 (34%)	1934 (26%)	29 522 (26%)
Missing	2313 (25%)	178 (25%)	260 (29%)	21 937 (25%)	1577 (26%)	2174 (30%)	28 439 (25%)
Referral type							
Self-referral	6037 (65%)	365 (51%)	516 (57%)	59 626 (67%)	3157 (51%)	4309 (59%)	74 010 (65%)
Referral by health centre	1959 (21%)	241 (34%)	222 (25%)	17 380 (20%)	2088 (34%)	1728 (24%)	23 618 (21%)
Missing	1251 (14%)	106 (15%)	163 (18%)	11 776 (13%)	946 (15%)	1284 (18%)	15 526 (14%)
Pneumonia in past 12 months							
No	8262 (89%)	623 (88%)	748 (83%)	66 047 (74%)	4612 (75%)	4991 (68%)	85 283 (75%)
Yes	223 (2%)	16 (2%)	25 (3%)	16 481 (19%)	1024 (17%)	1278 (18%)	19 047 (17%)
Missing	762 (8%)	73 (10%)	128 (14%)	6254 (7%)	555 (9%)	1052 (14%)	8824 (8%)
Previous hospital admission for pneumonia in past 12 months							
No	8333 (90%)	622 (87%)	754 (84%)	71 541 (81%)	4944 (80%)	5390 (74%)	91 584 (81%)
Yes	128 (1%)	13 (2%)	10 (1%)	10 777 (12%)	660 (11%)	816 (11%)	12 404 (11%)
Missing	786 (9%)	77 (11%)	137 (15%)	6464 (7%)	587 (10%)	1115 (15%)	9166 (8%)
Measles in past 2 months							
No	7914 (86%)	596 (84%)	681 (76%)	74 872 (84%)	5068 (82%)	5321 (73%)	94 452 (84%)
Yes	25 (<1%)	0	3 (<1%)	1182 (1%)	91 (2%)	121 (2%)	1422 (1%)
Missing	1308 (14%)	116 (16%)	217 (24%)	12 728 (14%)	1032 (17%)	1879 (26%)	17 280 (15%)

(Table 1 continues on next page)

	Younger than 2 months (n=10 860)			2–59 months (n=102 294)			Total (%) n=113 154
	Survived (%) n=9247	Died (%) n=712	Missing (%) n=901	Survived (%) n=88 782	Died (%) n=6191	Missing (%) n=7321	
(Continued from next page)							
Weight for age category							
Normal	7868 (85%)	472 (66%)	702 (78%)	64 641 (73%)	2765 (45%)	4784 (65%)	81 232 (72%)
Moderate underweight*	570 (6%)	107 (15%)	75 (8%)	11 939 (13%)	1208 (20%)	1028 (14%)	14 927 (13%)
Severe underweight*	248 (3%)	58 (8%)	23 (3%)	7097 (8%)	1338 (22%)	740 (10%)	9504 (8%)
Missing	561 (6%)	75 (11%)	101 (11%)	5105 (6%)	880 (14%)	769 (11%)	7491 (7%)
Severe acute malnutrition†							
Absent	7892 (85%)	578 (81%)	675 (75%)	74 570 (84%)	4649 (75%)	5269 (72%)	93 633 (83%)
Present	21 (<1%)	6 (1%)	5 (1%)	1047 (1%)	482 (8%)	151 (2%)	1712 (2%)
Missing	1334 (14%)	128 (18%)	221 (25%)	13 165 (15%)	1060 (17%)	1901 (26%)	17 809 (16%)
Temperature							
Afebrile	6488 (70%)	445 (63%)	604 (67%)	47 949 (54%)	3400 (55%)	3714 (51%)	62 600 (55%)
Febrile (>38°C)	1355 (15%)	143 (20%)	113 (13%)	27 105 (31%)	1699 (27%)	2139 (29%)	32 554 (29%)
Missing	1404 (15%)	124 (17%)	184 (20%)	13 728 (16%)	1092 (18%)	1468 (20%)	18 000 (16%)
Mean (SD, range), °C	37·3 (0·9, 30·0–42·2)	37·2 (1·5, 31·0–42·0)	37·3 (0·9, 33·5–41·1)	37·8 (1·2, 30·0–45·0)	37·7 (1·2, 30·7–42·0)	37·8 (1·2, 30·2–42·0)	37·8 (1·2, 30·0–45·0)
Median, °C (IQR)	37·2 (36·8–38·0)	37·2 (36·8–38·0)	37·1 (36·7–38·0)	37·8 (37·0–38·7)	37·8 (37·0–38·5)	37·8 (37·0–38·7)	37·8 (37·0–38·6)
Season							
Dry (May–October)	4206 (46%)	385 (54%)	439 (49%)	42 675 (48%)	3046 (49%)	3735 (51%)	54 486 (48%)
Wet (November–April)	5019 (54%)	326 (46%)	455 (51%)	45 925 (52%)	3124 (51)	3543 (48%)	58 392 (52%)
Missing	22 (<1%)	1 (<1%)	7 (1%)	182 (<1%)	21 (<1%)	43 (1%)	276 (<1%)
Respiratory rate							
Normal	1362 (15%)	83 (12%)	184 (20%)	4523 (5%)	364 (6%)	467 (6%)	6983 (6%)
Fast breathing‡	6903 (75%)	543 (76%)	543 (60%)	75 674 (85%)	5139 (83%)	5534 (76%)	94 336 (83%)
Missing	982 (11%)	86 (12%)	174 (19%)	8585 (10%)	688 (11%)	1320 (18%)	11 835 (11%)
Mean (SD, range)	67 (12·7, 2–198)	69 (14·2, 20–155)	65 (13·6, 2–180)	61 (12·3, 2–270)	64 (14·3, 5–180)	60 (13·3, 3–195)	62 (12·7, 2–270)
Median (IQR)	66 (61–72)	68 (62–75)	64 (59–70)	60 (54–68)	62 (56–70)	60 (52–67)	60 (54–68)
Malaria blood film status							
Negative	1103 (12%)	50 (7%)	79 (9%)	16 196 (18%)	974 (16%)	968 (13%)	19 370 (17%)
Positive	266 (3%)	17 (2%)	18 (2%)	7708 (9%)	562 (9%)	490 (7%)	9061 (8%)
Missing	7878 (85%)	645 (91%)	804 (89%)	64 878 (73%)	4655 (75%)	5863 (80%)	84 723 (75%)
HIV status							
Negative	643 (7%)	34 (5%)	68 (8%)	5441 (6%)	292 (5%)	448 (6%)	6926 (6%)
Positive	68 (1%)	7 (1%)	7 (1%)	1248 (1%)	241 (4%)	151 (2%)	1722 (2%)
Missing	8536 (92%)	671 (94%)	826 (92%)	82 093 (93%)	5658 (91%)	6722 (92%)	104 506 (92%)
Outcome§							
Died within 24 h of admission	0	404 (57%)	0	0	2966 (48%)	0	3370 (3%)
Died after 24 h of admission	0	308 (43%)	0	0	3225 (52%)	0	3533 (3%)
Left against advice	389 (4%)	0	0	2585 (3%)	0	0	2974 (3%)
Transferred	31 (<1%)	0	0	373 (<1%)	0	0	404 (<1%)
Discharged alive	8827 (96%)	0	0	85 824 (97%)	0	0	94 651 (84%)
Treatment failure at 48 h	0	0	5 (1%)	0	0	310 (4%)	315 (<1%)
Treatment failure at day 5	0	0	6 (1%)	0	0	160 (2%)	166 (<1%)
Missing	0	0	890 (99%)	0	0	6851 (94%)	7741 (7%)

Data are n (%) unless otherwise indicated. N/A=not appropriate. *Moderate undernutrition was defined as weight-for-age less than –2 SD from the mean based on the WHO 2006 growth reference standards; severe undernutrition was defined as weight-for-age less than –3 SD based on the WHO 2006 growth reference standards.[10] †The diagnosis of severe acute malnutrition was made prospectively during patient care by the health worker based on visible signs of severe wasting or oedema of both feet or by National Guidelines in Malawi.[8,10] ‡60 breaths per min of more if <2 months old, ≥50 breaths per min if 2–11 months old; 40 breaths per min or more if 12–59 months old. §Left against advice and Transferred are counted as Survived as the child did not die in the facility and we are only able to measure deaths in the facility (ie, calculate facility case fatality rate rather than population-level mortality). However, treatment failures are counted as missing for mortality as they are more likely to have died (although we do not have any data on this).

Table 1: **Study population characteristics**

factors of mortality included in the multivariable models, and key variables that were found to be predictors of missingness including region and type of facility. The HIV and malaria variables were excluded for having too many missing data to be imputed. Once we imputed the data in REALCOM, the data were uploaded into Stata for analysis using the commands "mi estimate: xtmelogit".[12]

We used separate logistic regression models to analyse the available data for HIV. Scenarios were generated to assess the effect of possible trends of HIV prevalence and case fatality rates in HIV-negative cases on overall case fatality rates, assuming odds of mortality in HIV-positive pneumonia cases 5·9 times higher than the odds of mortality in HIV-negative cases[17] in five scenarios and changing the odds in another scenario.

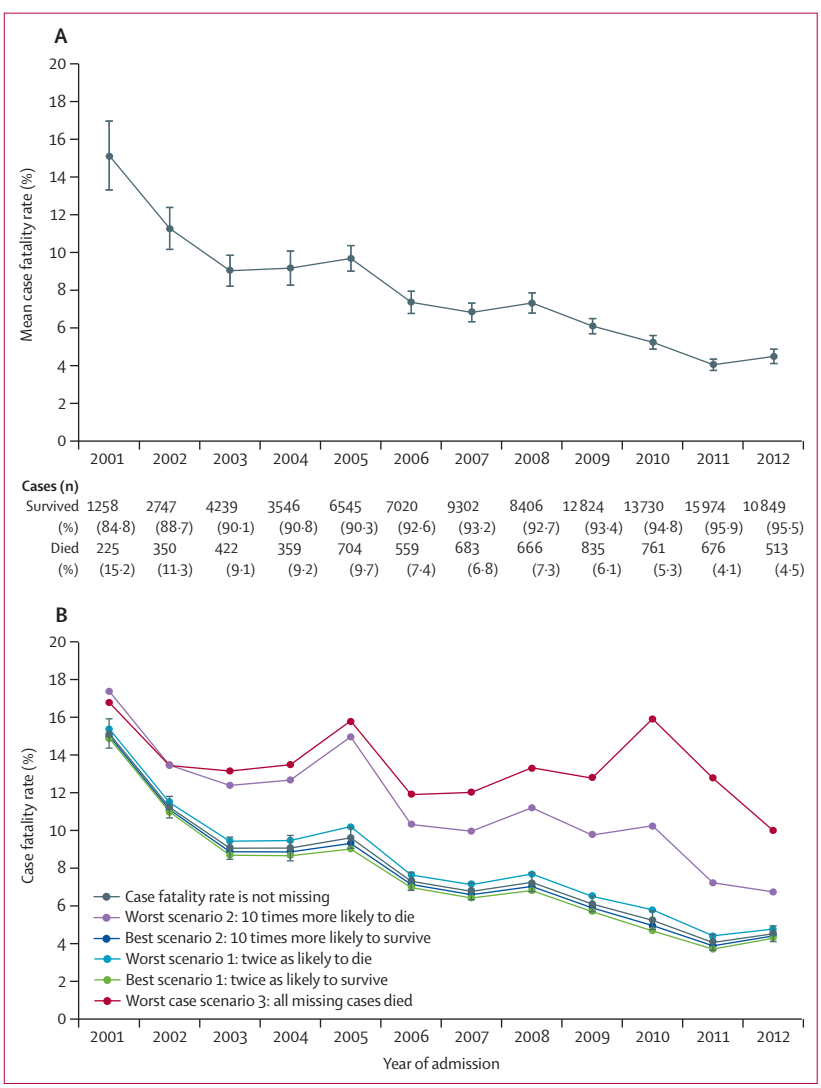

***Figure 2*: (A) Case fatality rate for children with pneumonia in Malawi (missing data not included) and (B) worst and best case scenario case fatality rates on the basis of different assumptions about case fatality for cases with missing data on fatality, 2001–12**
Error bars show 95% CI.

Role of the funding source
The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

All clinical pneumonia cases registered on the yellow forms with an age younger than 5 years were included (figure 1). Of the 113 154 unique cases within the dataset that were available for analysis (figure 1), 102 294 cases were aged 2–59 months and 10 860 cases were younger than 2 months. The number of cases with each potential risk factor in young infants and children who survived, died, or for whom data on case fatality were missing are listed in table 1. Overall, less than 20% of data were missing for all but three variables: previous antibiotic treatment (25·1% of data were missing), malaria blood film (74·8% of data were missing), and HIV status (92·3% of data were missing). The number of annual cases can be found in the appendix (p 6). District hospitals contributed the largest number of cases (appendix p 7).

6903 deaths were registered between 2001 and 2012, an overall case fatality rate of 6·6% (95% CI 6·4–6·7). The case fatality rate decreased with time (15·2% [13·4–17·1] in 2001 *vs* 4·5% [4·1–4·9] in 2012; $p_{trend}<0·0001$; figure 2), even when mortality was assumed to be ten times higher in cases for whom mortality data were missing than in cases with mortality data.

In the multivariable model, the following risk factors were significantly associated with high mortality in infants younger than 2 months (table 2): very severe pneumonia (compared with severe pneumonia); referral from a health centre (compared with self-referral); moderately underweight and severely underweight for age (compared with normal weight for age); and febrile temperature (compared with afebrile temperature). Wet season (compared with dry season), increasing year from 2001 to 2012, and increasing age (1 month of age compared with 0 months of age) were associated with lower mortality. Severe acute malnutrition, which was significantly associated with higher mortality, was the only significant variable in univariable analyses that was not included in the multivariable model.

In children aged 2–11 months, our findings were similar to those of young infants with respect to the above-cited risk factors (table 2). The following risk factors were also significantly associated with increased odds of mortality: location of hospital in the southern region; female sex; clinically suspected *Pneumocystis jirovecii* infection; more than 21 days with symptoms; and severe acute malnutrition. Fast breathing (compared with normal breathing) was the only additional factor associated with lower mortality in the multivariable model. Previous antibiotic treatment,

	Younger than 2 months		2–11 months		12–59 months	
	Univariable analyses OR (95% CI)	Multivariable model n=6878¶‖ AOR (95% CI)	Univariable analyses OR (95% CI)	Multivariable model n=34 427¶** AOR (95% CI)	Univariable analyses OR (95% CI)	Multivariable model n=28 952¶†† AOR (95% CI)
Geographical region of Malawi						
Northern	1·00	..	1·00	1·00	1·00	..
Central	1·00 (0·70–1·43)	..	1·00 (0·75–1·32)	1·10 (0·85–1·44)	1·21 (0·85–1·70)	..
Southern	0·94 (0·66–1·35)	..	1·50 (1·13–1·98)	1·42 (1·09–1·84)	1·37 (0·97–1·94)	..
Type of health-care facility						
District	1·00	..	1·00	..	1·00	..
Central	1·05 (0·75–1·47)	..	1·23 (0·94–1·60)	..	1·05 (0·78–1·42)	..
Mission/rural	1·13 (0·67–1·92)	..	1·34 (0·84–2·13)	..	0·77 (0·46–1·30)	..
Sex						
Male	1·00	..	1·00	1·00	1·00	1·00
Female	1·04 (0·89–1·22)	..	1·32 (1·24–1·41)	1·51 (1·38–1·65)	1·27 (1·16–1·41)	1·35 (1·18–1·54)
Pneumonia classification‡						
Non-severe	N/A	N/A	1·00	1·00	1·00	1·00
Severe	1·00	1·00	1·56 (1·01–2·43)	2·20 (1·02–4·71)	0·73 (0·48–1·09)	1·60 (0·74–3·43)
Very severe	4·11 (3·42–4·95)	3·60 (2·81–4·60)	9·44 (6·10–14·62)	12·22 (5·70–26·17)	4·30 (2·86–6·44)	9·38 (4·37–20·09)
Pneumocystis jirovecii	5·47 (1·55–19·33)	5·80 (0·71–47·38)	19·93 (11·72–33·89)	21·35 (8·86–51·46)	5·26 (2·25–12·30)	6·25 (1·62–24·05)
Days with symptoms						
<21 days	1·00	..	1·00	1·00	1·00	..
>21 days	1·10 (0·63–1·92)	..	1·99 (1·72–2·29)	1·35 (1·08–1·67)	2·36 (1·90–2·92)	..
Previous antibiotic treatment						
No	1·00	..	1·00	..	1·00	
Yes	1·14 (0·94–1·38)	..	1·48 (1·38–1·59)	..	1·66 (1·48–1·86)	..
Type of referral						
Self-referral	1·00	1·00	1·00	1·00	1·00	1·00
From health centre	2·02 (1·70–2·41)	1·85 (1·50–2·29)	2·02 (1·88–2·17)	1·72 (1·56–1·88)	2·85 (2·55–3·18)	2·23 (1·94–2·57)
Previous pneumonia in past 12 months						
No	1·00	..	1·00	..	1·00	..
Yes	0·96 (0·58–1·62)	..	1·09 (1·00–1·19)	..	0·86 (0·76–0·98)	..
Previous hospital admission due to pneumonia						
No	1·00	..	1·00	..	1·00	..
Yes	1·39 (0·78, 2·48)	..	1·17 (1·05–1·30)	..	0·83 (0·72–0·96)	..
Measles in past 2 months						
No	*	..	1·00	1·00	1·00	..
Yes	*	..	1·19 (0·93–1·52)	1·31 (0·92–1·87)	0·87 (0·55–1·37)	..
Weight for age						
Normal weight	1·00	1·00	1·00	1·00	1·00	1·00
Moderately underweight	3·20 (2·55–4·03)	3·37 (2·54–4·47)	2·60 (2·39–2·82)	2·27 (2·04–2·53)	2·07 (1·80–2·37)	1·70 (1·43–2·02)
Severely underweight	3·82 (2·82–5·18)	3·76 (2·56–5·53)	4·24 (3·89–4·62)	3·42 (3·04–3·85)	5·00 (4·40–5·68)	3·23 (2·72–3·84)
Severe acute malnutrition						
Absent	1·00	..	1·00	1·00	1·00	1·00
Present	3·91 (1·55, 9·86)	..	6·62 (5·63–7·79)	2·85 (2·18–3·75)	10·04 (8·51–11·84)	4·19 (3·28–5·35)
Malaria blood film positive						
No	1·00	†	1·00	†	1·00	†
Yes	1·47 (0·82–2·65)	†	1·03 (0·90–1·18)	†	1·52 (1·27–1·83)	†
HIV status						
Negative	1·00	†	1·00	†	1·00	†
Positive	1·95 (0·83–4·56)	†	3·93 (3·11–4·96)	†	3·43 (2·51–4·69)	†
Body temperature						
Afebrile	1·00	1·00	1·00	..	1·00	..
Febrile (>38°C)	1·56 (1·28–1·91)	1·52 (1·20–1·93)	0·94 (0·87–1·01)	..	0·83 (0·75–0·93)	..

(Table 2 continues on next page)

	Younger than 2 months		2–11 months		12–59 months	
	Univariable analyses OR (95% CI)	Multivariable model n=6878¶|| AOR (95% CI)	Univariable analyses OR (95% CI)	Multivariable model n=34 427¶** AOR (95% CI)	Univariable analyses OR (95% CI)	Multivariable model n=28 952¶†† AOR (95% CI)
(Continued from previous page)						
Season						
Dry (May–October)	1·00	1·00	1·00	..	1·00	1·00
Wet (November–April)	0·71 (0·60–0·82)	0·72 (0·59–0·88)	0·90 (0·85–0·96)	..	1·08 (0·98–1·20)	1·57 (1·01–1·32)
Respiratory category						
Normal	1·00	..	1·00	1·00	1·00	..
Fast breathing§	1·27 (1·00–1·61)	..	1·05 (0·93–1·18)	0·80 (0·67–0·95)	0·79 (0·59–1·06)	..
Year admitted to hospital per year, 2001–12	0·886 (0·861–0·911)	0·909 (0·876–0·944)	0·888 (0·878–0·898)	0·915 (0·900–0·929)	0·885 (0·870, 0·901)	0·915 (0·893–0·938)
Age, months	0·563 (0·480–0·660)	0·567 (0·458–0·703)	0·954 (0·943–0·965)	0·947 (0·932 – 0·963)	0·991 (0·986, 0·996)	..

OR=odds ratio. AOR=adjusted odds ratio. ..=data not included in final multivariable model. N/A=not applicable. *Model did not converge because none of the cases that died had measles (and only 25 cases of measles in total). †Not entered into multivariable model building process as too much missing data. ‡See panel for definitions. §More than 60 breaths per min for children younger than 2 months; 50 breaths per min or more for children 2–11 months old; and 40 breaths per min for children 12–59 months old. ¶Number of cases in multivariable model are less than total number of cases because of missing data for one or more variables in the model. ||445 deaths; nine variables; 49 events per variable; area under ROC curve 0·77. **2520 deaths, 15 variables, 168 events per variable; area under ROC curve 0·81. ††1004 deaths; ten variables, 100 events per variable; area under ROC curve 0·83.

Table 2: **Univariable analyses and mixed effects multivariable regression analysis showing odds ratio (95% CI) for risk factors for mortality in children younger than 2 months, 2–11 months of age, and 12–59 months of age**

previous hospital admission with pneumonia, and HIV-positive status were significantly associated with increased mortality in univariable analyses but not included in the multivariable model.

Findings in children aged 12–59 months were similar to those in children age 2–11 months, although region, number of days with symptoms, measles in the past 2 months, and respiratory category were not in the multivariable model whereas season was, with wet season significantly associated with higher mortality (table 2).

Results from the multiple imputation models indicated that missing data had little effect on the estimates from the complete case analysis. Only the association of clinically diagnosed *P jirovecii* with mortality in children younger than 2 months was statistically significant with multiple imputation, whereas this risk factor was not statistically significant without multiple imputation (appendix p 22 and table 2).

Between 2001 and 2012, the proportion of children with characteristics associated with a higher odds of mortality decreased; these characteristics included very severe pneumonia of any age group, children 2–59 months old with moderate and severe underweight for age, and children receiving antibiotics before admission to hospital (table 3). During this period, the proportion of children with characteristics associated with lower odds of death (children diagnosed or admitted to hospital with pneumonia in the past year) increased.

Overall, we found the same decreasing trend in mortality when cases where stratified by age, region, hospital type, sex, pneumonia severity, weight-for-age, duration of illness, type of access to hospital, previous treatment, prior history of pneumonia or hospital admission, and HIV status (table 4, appendix pp 8–21). Despite this progress, case fatality rates in 2012 remained high for children of all ages with very severe pneumonia (11·8%; 10·3% for infants younger than 2 months, 16·5% for infants aged 2–11 months, and 6·1% for children aged 12–59 months), severe undernutrition (15·4%), and severe acute malnutrition (34·8%), and for children with symptoms lasting more than 21 days (9·0%;).

The additional logistic regression model used with the available HIV data showed that the reduction in pneumonia mortality per year was statistically significant even if HIV status was included in the model (AOR of mortality per year 0·89 [95% CI 0·85–0·93], p<0·0001, n=7842). When using the conservative assumption that all cases missing HIV data were HIV-negative, this result remains significant (AOR of mortality per year 0·883 [0·875–0·892], p<0·0001, n=103 184).

The possible effects on pneumonia case fatality rates of changes in HIV prevalence with time are shown in the appendix (p 30). None of the scenarios supported the hypothesis that the decrease in pneumonia case fatality rate can predominantly be explained by a decrease in HIV prevalence.

Discussion

Our study shows that overall mortality for children admitted to hospital with pneumonia in Malawi has significantly decreased between 2001 and 2012. The decrease in case fatality rate was gradual and consistent across regions, hospital types, sex, age, pneumonia severity, type of access to hospital, type of previous treatment, and previous history of pneumonia or hospital

	Year of study												Slope (SE); p_{trend}
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
Female sex	674 (44·3%; 41·9–46·9)	1516 (47·4%; 45·7–49·1)	2334 (47·7%; 46·3–49·1)	1877 (46·0%; 44·5–47·5)	3449 (45·4%; 44·3–46·5)	3493 (44·7%; 43·6–45·8)	4758 (46·2%; 45·2–47·1)	4268 (44·9%; 43·9–45·9)	6522 (45·4%; 44·7–46·3)	6907 (43·5%; 42·8–44·3)	7878 (44·2%; 43·5–44·9)	5131 (43·5%; 42·6–44·4)	−0·3% (0·1%); p<0·0001
Young infants (<2 months)	110 (7·2%; 6·0–8·6)	230 (7·2%; 6·3–8·1)	514 (10·4%; 9·6–11·3)	371 (9·0%; 8·8–10·1)	735 (9·5%; 8·8–10·1)	946 (11·8%; 11·2–12·6)	1388 (13·1%; 12·5–13·8)	817 (8·4%; 7·9–9·0)	1591 (10·8%; 10·3–11·3)	1331 (8·2%; 7·8–8·6)	1675 (9·2%; 8·8–9·6)	930 (7·7%; 7·3–8·2)	−0·1% (0·03%); p<0·0001
Very severe pneumonia													
Age 2–59 months	431 (30·7%; 28·4–33·2)	989 (33·5%; 31·8–35·3)	1281 (29·2%; 27·9–30·5)	1054 (28·4%; 27·0–29·9)	1981 (28·4%; 27·4–29·5)	1863 (26·7%; 25·7–27·8)	2415 (26·6%; 25·7–27·6)	2266 (25·9%; 25·0–26·8)	3143 (24·2%; 23·5–24·9)	3095 (21·0%; 20·3–21·6)	3348 (20·4%; 19·8–21·0)	2604 (23·7%; 22·9–24·5)	−1·0% (0·1%); p<0·0001
Age <2 months	77 (70·6%; 61·4–78·5)	158 (70·9%; 64·5–76·5)	295 (57·8%; 53·5–62·1)	195 (53·4%; 48·3–58·5)	413 (57·7%; 54·0–61·3)	478 (51·3%; 48·1–54·5)	691 (50·8%; (48·1–53·4)	410 (50·7%; 47·2–54·1)	687 (43·6%; 41·2–46·1)	492 (37·8%; 35·2–40·5)	613 (37·4%; 35·1–39·8)	340 (37·4%; 34·4–40·6)	−2·9% (0·2%); p<0·0001
Weight-for-age													
Moderately underweight*	264 (17·4%; 15·5–19·3)	610 (19·0%; 17·6–19·3)	810 (16·5%; 15·4–17·5)	680 (16·5%; 15·4–17·7)	1142 (14·7%; 13·9–15·5)	1148 (14·4%; 13·6–15·2)	1414 (13·3%; 12·7–14·0)	1314 (13·6%; 12·9–14·3)	1850 (12·6%; 12·1–13·1)	1994 (12·3%; 11·8–12·8)	2068 (11·3%; 10·9–11·8)	1400 (11·6%; 11·1–12·2)	−0·6% (0·03% <0·0001
Severely underweight*	182 (12·0%; 10·4–13·7)	458 (14·2%; 13·1–15·5)	573 (11·6%; 10·8–12·6)	503 (12·2%; 11·2–13·2)	863 (11·1%; 10·4–11·8)	838 (10·5%; 9·8–11·2)	915 (8·6%; 8·1–9·2)	872 (9·0%; 8·4–9·6)	1162 (7·9%; 7·5–8·4)	1119 (6·9%; 6·5–7·3)	1131 (6·2%; 5·8–6·5)	727 (6·0%; 5·6–6·5)	−0·7% (0·03%); <0·0001
Severe acute malnutrition†	70 (5·2%; 4·2–6·6)	187 (6·1%; 5·3–7·0)	174 (3·8%; 3·2–4·3)	90 (2·4%; 2·0–3·0)	152 (2·2%; 1·9–2·6)	128 (1·8%; 1·5–2·1)	198 (2·1%; 1·9–2·5)	137 (1·6%; 1·4–1·9)	193 (1·5%; 1·3–1·8)	166 (1·3%; 1·1–1·5)	116 (0·8%; 0·7–0·9)	75 (0·8%; 0·6–1·0)	−0·3% (0·02%) <0·0001
Symptoms for >21 days	44 (3·0%; 2·2–4·0)	70 (2·2%; 1·8–2·8)	125 (2·7%; 2·3–3·2)	150 (3·9%; 3·3–4·6)	291 (4·1%; 3·7–4·6)	248 (3·4%; 3·0–3·8)	341 (3·5%; 3·2–3·9)	327 (3·6%; 3·3–4·1)	414 (3·0%; 2·8–3·3)	381 (2·6%; 2·3–2·8)	336 (2·1%; 1·8–2·3)	282 (2·6%; 2·3–2·9)	−0·1% (0·02%); <0·0001
Self-referral to hospital	1134 (77·8%; 75·6–79·9)	2429 (78·9%; 77·5–80·3)	3390 (76·0%; 74·7–77·2)	2725 (73·5%; 72·0–74·9)	5145 (75·4%; 74·4–76·4)	5194 (73·6%; 72·5–74·6)	6770 (73·1%; 72·2–74·0)	6279 (75·2%; 74·2–76·1)	9822 (76·1%; 75·4–76·9)	10506 (75·7%; 74·9–76·4)	11787 (76·8%; 76·1–77·4)	7970 (7·89%; 78·1–79·7)	−0·2% (0·05%); <0·0001
No antibiotic before hospital admission	1022 (73·5%; 71·1–75·8)	2103 (75·4%; 73·7–76·9)	2818 (69·5%; 68·1–70·9)	2187 (67·1%; 65·5–68·7)	4240 (68·3%; 67·2–69·5)	3765 (61·8%; 60·3–62·8)	5035 (62·6%; 61·6–63·7)	4722 (65·5%; 64·4–66·6)	7358 (64·5%; 63·6–65·3)	7637 (63·6%; 62·7–64·5)	8020 (63·0%; 62·2–63·9)	5730 (66·6%; 65·6–67·6)	-0·6% (0·1%); <0·0001
Pneumonia in past 12 months	238 (15·8%; 14·1–17·8)	498 (15·6%; 14·4–16·9)	655 (13·8%; 12·8–14·8)	657 (16·7%; 15·6–17·9)	1372 (19·2%; 18·3–20·1)	1248 (16·2%; 15·4–17·0)	1700 (17·1%; 16·4–17·9)	1749 (19·1%; 18·3–19·9)	2372 (17·3%; 16·6–17·9)	2757 (18·6%; (18·0–19·3)	3253 (20·2%; 19·6–20·8)	2278 (21·0%; 20·2–21·8)	0·5% (0·04%); <0·0001
Hospital admission in past 12 months	135 (9·0%; 7·6–10·5)	302 (9·5%; 8·5–10·6)	387 (8·2%; 7·4–9·0)	408 (10·4%; 9·5–11·4)	872 (12·2%; 11·5–13·0)	882 (11·5%; 10·8–12·2)	1128 (11·4%; 10·8–12·0)	1172 (12·8%; 12·2–13·5)	1532 (11·2%; 10·7–11·7)	1575 (10·7%; 10·2–11·2)	2268 (14·1%; 13·6–14·7)	1557 (14·3%; 13·7–15·0)	0·4% (0·04%); <0·0001
Measles in past 2 months	11 (0·8%; 0·4–1·4)	17 (0·6%; 0·3–0·9)	18 (0·4%; 0·2–0·6)	13 (0·4%; (0·2–0·6)	34 (0·5%; (0·3–0·7)	43 (0·6%; 0·4–0·8)	57 (0·6%; 0·5–0·8)	71 (0·8%) (0·7–1·0)	125 (1·0%; 0·8–1·2)	749 (5·7%; 5·3–6·1)	186 (1·3%; 1·1–1·5)	70 (0·7%; 0·6–0·9)	0·2% (0·01%); <0·0001

Data are n (%; 95% CI of the proportion). Only variables with less than 20% missing data are included in the analysis, with the exception of antibiotic treatment before hospital admission (rate of missing data 25%); p_{trend} was calculated for 2001–12. *Moderate undernutrition was defined as weight-for-age less than −2 SD from the mean based on the WHO 2006 growth reference standards; severe undernutrition was defined as weight-for-age less than −3 SD based on the WHO 2006 growth reference standards.[10] †The diagnosis of severe acute malnutrition was made prospectively during patient care by the health worker based on visible signs of severe wasting or oedema of both feet or by National Guidelines in Malawi.[8,10]

Table 3: **Percentage of children presenting with possible factors affecting the risk of pneumonia mortality, by study year**

admission. Furthermore, the association of decreasing case fatality rate by study year was statistically significant in our multivariable models for each age group. In parallel, the prevalence of mortality risk factors (very severe pneumonia and malnutrition) decreased, and the prevalence of potentially protective factors increased. Despite this progress, we saw no significant decrease in mortality for some categories of children, such as

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Region												
Northern	92 (17%)	75 (11%)	88 (9%)	102 (10%)	137 (8%)	132 (7%)	123 (6%)	90 (5%)	127 (5%)	84 (4%)	72 (3%)	45 (3%)
Central	74 (16%)	157 (11%)	165 (8%)	129 (10%)	349 (12%)	302 (9%)	239 (5%)	213 (6%)	300 (6%)	312 (5%)	251 (3%)	207 (4%)
Southern	59 (13%)	118 (13%)	169 (10%)	128 (9%)	218 (9%)	125 (6%)	321 (10%)	363 (10%)	408 (7%)	365 (7%)	353 (5%)	261 (5%)
Hospital												
Mission	2 (13%)	4 (50%)	1 (25%)	3 (15%)	20 (13%)	39 (13%)	119 (7%)	153 (7%)	150 (6%)	97 (6%)	70 (4%)	40 (5%)
District	223 (15%)	344 (11%)	394 (9%)	350 (9%)	545 (9%)	453 (7%)	492 (7%)	441 (7%)	649 (6%)	583 (5%)	543 (4%)	431 (4%)
Central	0	2 (50%)	27 (16%)	6 (8%)	139 (11%)	67 (10%)	72 (6%)	72 (9%)	36 (5%)	81 (5%)	63 (3%)	42 (6%)
Sex												
Male	111 (13%)	166 (10%)	206 (8%)	182 (9%)	349 (9%)	258 (6%)	337 (7%)	323 (7%)	397 (6%)	371 (5%)	320 (4%)	255 (4%)
Female	114 (18%)	183 (13%)	213 (10%)	171 (10%)	336 (11%)	284 (9%)	326 (7%)	330 (8%)	411 (7%)	366 (6%)	341 (5%)	244 (5%)
Age												
<2 months	23 (21%)	28 (12%)	60 (12%)	34 (10%)	66 (10%)	77 (9%)	96 (7%)	57 (8%)	74 (5%)	67 (6%)	64 (4%)	53 (6%)
2–59 months	202 (15%)	322 (11%)	362 (9%)	325 (9%)	638 (10%)	482 (7%)	587 (7%)	609 (7%)	761 (6%)	694 (5%)	612 (4%)	460 (4%)
Severity												
Very severe, 2–59 months	121 (29%)	224 (24%)	257 (21%)	204 (20%)	402 (21%)	274 (15%)	371 (16%)	381 (18%)	450 (16%)	383 (14%)	368 (12%)	289 (12%)
Severe, 2–59 months	74 (8%)	91 (5%)	97 (4%)	112 (5%)	210 (5%)	191 (4%)	187 (3%)	214 (4%)	298 (3%)	292 (3%)	230 (2%)	159 (2%)
Very severe, <2 months	23 (30%)	24 (15%)	47 (17%)	30 (16%)	52 (13%)	57 (13%)	69 (10%)	42 (11%)	58 (9%)	43 (10%)	44 (8%)	33 (10%)
Severe, <2 months	0	4 (6%)	12 (6%)	4 (2%)	12 (5%)	19 (5%)	23 (4%)	14 (4%)	16 (2%)	21 (3%)	17 (2%)	17 (3%)
Weight												
Normal	131 (12%)	184 (9%)	254 (8%)	199 (7%)	404 (8%)	323 (6%)	425 (5%)	417 (6%)	524 (5%)	493 (4%)	422 (3%)	317 (3%)
Moderately underweight	60 (24%)	81 (14%)	83 (11%)	72 (11%)	146 (14%)	112 (10%)	113 (9%)	124 (10%)	144 (8%)	131 (7%)	130 (7%)	92 (7%)
Severely underweight	34 (19%)	85 (20%)	85 (16%)	88 (19%)	154 (20%)	124 (16%)	145 (17%)	125 (15%)	167 (16%)	137 (14%)	124 (12%)	104 (15%)
Malnutrition												
Severe acute malnutrition	22 (34%)	45 (26%)	46 (28%)	31 (36%)	47 (34%)	34 (28%)	56 (31%)	43 (34%)	76 (45%)	41 (30%)	19 (18%)	24 (35%)
Days with symptoms												
<21 days	208 (15%)	333 (11%)	374 (9%)	302 (9%)	600 (9%)	477 (7%)	570 (7%)	566 (7%)	720 (6%)	645 (5%)	572 (4%)	432 (4%)
>21 days	12 (29%)	9 (14%)	16 (14%)	20 (14%)	49 (18%)	34 (15%)	37 (12%)	31 (10%)	48 (13%)	46 (14%)	17 (6%)	23 (9%)
Type of referral												
Self-referral	131 (12%)	207 (9%)	244 (8%)	216 (8%)	386 (8%)	296 (6%)	356 (6%)	304 (5%)	394 (4%)	368 (4%)	315 (3%)	247 (3%)
Referred from a health centre	83 (26%)	120 (19%)	132 (13%)	93 (10%)	236 (15%)	180 (10%)	230 (10%)	253 (13%)	297 (11%)	265 (9%)	231 (7%)	181 (9%)
Previous treatment												
No previous antibiotic	126 (13%)	209 (10%)	243 (9%)	169 (8%)	328 (8%)	236 (7%)	287 (6%)	251 (6%)	287 (4%)	319 (5%)	225 (3%)	173 (3%)
Previous antibiotic	74 (21%)	105 (16%)	114 (10%)	106 (10%)	227 (12%)	181 (8%)	217 (8%)	224 (10%)	314 (8%)	244 (6%)	246 (6%)	174 (7%)
Previous pneumonia in the past 12 months												
No	189 (15%)	296 (11%)	339 (9%)	286 (9%)	525 (10%)	451 (7%)	507 (7%)	519 (8%)	629 (6%)	539 (5%)	489 (4%)	370 (5%)
Yes	33 (14%)	49 (10%)	65 (10%)	51 (8%)	111 (9%)	80 (7%)	118 (7%)	86 (5%)	135 (6%)	132 (5%)	98 (3%)	71 (3%)
Admission to hospital for pneumonia in the last 12 months												
No	203 (15%)	319 (12%)	361 (9%)	302 (9%)	556 (9%)	470 (7%)	551 (7%)	541 (7%)	666 (6%)	570 (5%)	526 (4%)	403 (5%)
Yes	19 (15%)	26 (9%)	44 (12%)	34 (9%)	71 (9%)	58 (7%)	68 (6%)	63 (6%)	90 (6%)	94 (7%)	59 (3%)	40 (3%)
HIV status												
Negative	0	0	3 (6%)	3 (8%)	10 (9%)	22 (9%)	35 (6%)	56 (7%)	74 (6%)	55 (5%)	39 (3%)	21 (4%)
Positive	0	1 (50 %)	0	2 (13%)	15 (21%)	24 (23%)	33 (16%)	38 (19%)	57 (21%)	29 (12%)	27 (11%)	16 (10%)

Data are n (%) of cases recorded to have died in hospital (see appendix pp 8–21 for graphs of this data and n (%) of cases recorded to have survived).

Table 4: **Case fatality rates for key categories of potential risk factors for pneumonia mortality in Malawian hospitals, 2001–12**

children with very severe pneumonia, severe undernutrition, severe acute malnutrition, and symptoms lasting more than 21 days. Our findings also suggest possible sex inequality (girls had higher case fatality rates than boys) and regional disparities (southern Malawi with a higher mortality than other regions).

Several factors might have affected our results. The retrospective nature of this study might have biased results in several ways. First, variables were limited to those routinely collected on the yellow form whereas information on other potentially important factors such as vaccination status and socioeconomic condition, or height

of children (for a better assessment of nutritional status) were not available. Second, selection bias is possible; the study sample excluded a few smaller facilities, and a proportion of pneumonia cases in each facility might have been missed, or records could have been lost. Given that it is not possible to trace these cases, we do not know how these factors affected our case fatality results. In a routine setting such as this study, indicators such as prior antibiotic treatment and previous pneumonia relied only on verbal report; measurement of temperature, respiratory rate, and weight might have been affected by equipment accuracy, measurement error, or both.

Case fatality rates might have been affected either by misrecording of deaths (numerator) or misrecording of total pneumonia cases (denominator). Selective under-recording of deaths, with case selection towards more healthy cases, might have occurred for cases of very severe pneumonia dying only a few hours after hospital admission, or for other reasons. To this end we found a significant increase in the proportion of cases with unknown outcome over time (appendix, p 24). However, even assuming a worst case scenario where all cases with an unknown outcome were ten times more likely to die than cases with outcome recorded, the trend of decreasing case fatality rate was still observed (figure 2). The multivariable logistic regression models with multiple imputation also support a decreasing case fatality rate (appendix, p 22). That pneumonia misdiagnoses might have occurred is possible; however, misdiagnoses are unlikely to have systematically increased over time to the extent of explaining the observed trends in case fatality rate reductions. Case definition did not change with time—although it changed later (WHO revised the pneumonia classification criteria in 2013)—and data quality efforts were made during this time period.[6]

In terms of quality of data, we note significant increases in the percentage of cases with missing data with time, both on non-clinical variables and on variables necessitating patient measurement (appendix, pp 26–29); however, in the latter case these trends appear to be independent of case severity. These findings might suggest that the data quality decreased over time, perhaps due to the transition away from external support.

Despite these limitations, the study has the strength of representing a large sample from many hospitals in Malawi during a long period of time. Overall, our findings are consistent with the results of a recent systematic review,[3] in which the case fatality rate for children admitted to hospital with pneumonia in the African region was shown to be 3·9% (95% CI 2·7–5·5). According to a previous analysis of 24 hospitals using the yellow forms, case fatality rates for pneumonia in children had fallen from 18·6% in 2000 to 8·4% in 2005.[6] No other studies from sub-Saharan Africa report on trends of case fatality rates for hospital admissions for pneumonia over such a long period. In a review[18] of trends in overall mortality from respiratory diseases in Latin America between 1998 and 2009, investigators reported that mortality in children younger than 5 years had also significantly decreased. The results of this study are in line with the progress documented by official country indicators of Malawi (appendix, p 31), showing an improvement in many socioeconomic and health indicators. Several factors might have contributed to these achievements: extensive external support provided by CLHP between 2000 and 2008 (training, supervision, and supply of antibiotic drugs);[6] improved use of oxygen therapy;[19] strengthened community-case management;[20] and scale-up of antiretroviral drugs for HIV treatment.[21,22]

Overall, our multivariable results are mainly in line with previous analyses from low-income and middle-income countries in Africa and Asia. Severity of pneumonia, malnutrition, and young age are well known risk factors for pneumonia mortality.[23] In a systematic review[23] of 23 studies (20 835 children), female sex was associated with a 15% increase in the risk of death. The association between clinically suspected *P jirovecii* pneumonia and high risk of death has been confirmed in other studies.[24–26] Longer symptom duration has also been associated with higher mortality in Central African Republic, Zimbabwe, and Papua New Guinea,[27–29] and seasonality in pneumonia mortality has been observed in a nearby country (Kenya),[30] and might be explained by a higher prevalence of non-severe viral infections in a certain part of the year or by other factors.[31] Our finding of lower mortality in children (2–11 months of age) with fast breathing, after adjusting for confounders, could suggest that these children are less severely ill than those without fast breathing, an observation consistent with other studies in the Central African Republic[27] and Indonesia.[32]

The observation that children referred to hospital from a health centre were more likely to die than those who were not referred could have multiple explanations: more severe cases might tend to seek care at the nearest facility, usually a health centre, rather than directly travelling longer distances to the closest hospital, or incorrect outpatient treatment, including delayed referral, might affect mortality. Findings on fever should be interpreted in view of temperature being recorded only once at time of admission to hospital.

Results from this study have implications for practice by emphasising the importance of effective national systems of data collection. Importantly, results from this database, which contains only cases of hospitalised pneumonia, cannot be generalised to the epidemiology of pneumonia mortality in the community, which is estimated to be greater.[3] Large projects, including both hospital-based and community-based data are needed to estimate the overall risk of mortality from pneumonia in children in Malawi.

Despite these encouraging findings, our analysis also reveals areas for priority action. Case fatality rates for hospitalised pneumonia in Malawi remain high for

children with very severe pneumonia, malnutrition, long duration of symptoms, and young age. A high case fatality rate for hospitalised pneumonia in girls compared with boys, with a lower number of girls than boys admitted to hospital, suggests possible sex inequalities in access to care or quality of treatment. This aspect, together with regional differences in case fatality rates, deserves further assessment. The high proportion of children accessing the hospital through self-referral (78%), suggests that more needs to be done to strengthen primary health-care services and to improve coordination between levels of care.

Contributors

ML designed this study with major inputs from NL, TC, NS, GM, BN, and AC. ML, NL, RB, SS, GM, and CM were involved in data collection in Malawi. NS was responsible for data cleaning, which was checked by TC. ML and NS did the descriptive and univariable mortality analyses, NS did the multivariable and multiple imputation analyses, and TC checked all analyses. ML wrote the first draft of the Article, with major contributions from TC, AC, NL, BN, NS, and EDM. All authors reviewed subsequent drafts and agreed on the final version of this paper.

Declaration of interests

We declare no competing interests.

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References

1 Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015; **385:** 430–40.

2 Fischer Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013; **381:** 1405–16.

3 Nair H, Simıes EAF, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013; **381:** 1380–90.

4 Tornheim JA, Manya AS, Oyando N, Kabaka S, Breiman RF, Feikin DR. The epidemiology of hospitalized pneumonia in rural Kenya: the potential of surveillance data in setting public health priorities. *Int J Infect Dis* 2007; **11:** 536–43.

5 WHO. Millennium Development Goals (MDGs). WHO fact sheet n° 290. May, 2014. http://www.who.int/mediacentre/factsheets/fs290/en/ (accessed Oct 21, 2014).

6 Enarson PM, Gie R, Enarson DA, Mwansambo C. Development and Implementation of a National Programme for the Management of Severe and Very Severe Pneumonia in Children in Malawi. *PLoS Med* 2009; **6:** e1000137.

7 Enarson PM, Gie RP, Mwansambo CC, et al. Reducing deaths from severe pneumonia in children in Malawi by improving delivery of pneumonia case management. *PLoS One* 2014; **9:** e102955.

8 Ministry of Health, Government of the Republic of Malawi. Management of children with pneumonia (National Guidelines). Lilongwe: Government of the Republic of Malawi, 2000.

9 WHO. Management of the child with a serious infection or severe malnutrition. Guideline for care at the first referral level in developing countries. Geneva: Department of Child and Adolescent Health and Development, World Health Organization, 2000.

10 WHO. Pocket book of Hospital care for children. Guidelines for the management of common illnesses with limited resources. Geneva: World Health Organization, 2005.

11 WHO Multicentre Growth Reference Study Group. WHO child growth standards: methods and development. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva: World Health Organization, 2006.

12 Statacorp. Stata statistical software: release 13. College Station, TX: StataCorp LP, 2013.

13 Sauerbrei W. The use of resampling methods to simplify regression models in medical statistics. *Appl Stat* 1999; **48:** 313–29.

14 Royston P, Sauerbrei W. Bootstrap assessment of the stability of multivariable models. *Stata J* 2009; **9:** 547–70.

15 Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49:** 1373–79.

16 Carpenter J, Goldstein H, Kenward M. REALCOM-IMPUTE software for multilevel multiple imputation with mixed response types. *J Stat Softw* 2011; **45:** 1–14.

17 Theodoratou E, McAllister DA, Reed C, et al. Global, regional, and national estimates of pneumonia burden in HIV-infected children in 2010: a meta-analysis and modelling study. *Lancet Infect Dis* 2014; **14:** 1250–58.

18 de Souza MdFM, Widdowson M-A, Alencar AP, et al. Trends in mortality from respiratory disease in Latin America since 1998 and the impact of the 2009 influenza pandemic. *Bull World Health Organ* 2013; **91:** 525–32.

19 Enarson P, La VS, Gie R, Magangad E, Chokanie C. Implementation of an oxygen concentrator system in district hospital paediatric wards throughout Malawi. *Bull World Health Organ* 2008; **86:** 344–48.

20 Nsona H, Mtimuni A, Daelmans B, et al. Scaling up integrated community case management of childhood illness: update from Malawi. *Am J Trop Med Hyg* 2012; **87** (suppl 5)**:** 54–60.

21 Harries A, Makombe S, Libamba E, Schouten EJ. Why did the scale-up of HIV treatment work? A case example from Malawi. *J Acquir Immune Defic Syndr* 2011; **2011:** S64–67.

22 Mwagomba B, Zachariah R, Massaquoi M, et al. Mortality reduction associated with HIV/AIDS care and antiretroviral treatment in rural Malawi: evidence from registers, coffin sales and funerals. *PLoS One* 2010; **5:** e10452.

23 Sonego M, Pellegrin MC, Becker G, Lazzerini M. Risk factors for mortality from acute lower respiratory infections (ALRI) in children under five years of age in low and middle-income countries: a systematic review and meta-analysis of observational studies. *PLoS One* 2015; **10:** e0116380.

24 Graham SM, Mankhambo L, Phiri A, et al. Impact of human immunodeficiency virus infection on the etiology and outcome of severe pneumonia in Malawian children. *Pediatr Infect Dis J* 2011; **30:** 1–6.

25 Morrow BM, Hsaio N-Y, Zampoli M, Whitelaw A, Zar HJ. Pneumocystis pneumonia in South African children with and without human immunodeficiency virus infection in the era of highly active antiretroviral therapy. *Pediatr Infect Dis J* 2010; **29:** 535–39.

26 Zar H, Hanslo D, Tannenbaum E, et al. Aetiology and outcome of pneumonia in human immunodeficiency virus-infected children hospitalized in South Africa. *Acta Paediatr* 2001; **90**: 119–25.

27 Demers A-M, Morency P, Mberyo-Yaah F, et al. Risk factors for mortality among children hospitalized because of acute respiratory infections in Bangui, Central African Republic. *Pediatr Infect Dis J* 2000; **19:** 424–32.

28 Nathoo KJ, Nkrumah FK, Ndlovu D, Nhembe M, Pirie DJ, Kowo H. Acute lower respiratory tract infection in hospitalized children in Zimbabwe. *Ann Trop Paediatr* 1993; **13:** 253–61.

29 Duke T, Mgone J, Frank D. Hypoxaemia in children with severe pneumonia in Papua New Guinea. *Int J Tuberc Lung Dis* 2001; **5:** 511–19.

30 Ye Y, Zulu E, Mutisya M, Orindi B, Emina J, Kyobutungi C. Seasonal pattern of pneumonia mortality among under-five children in Nairobi's informal settlements. *Am J Trop Med Hyg* 2009; **81:** 770–75.

31 Berkley JA, Munywoki P, Ngama M, et al. Viral etiology of severe pneumonia among Kenyan infants and children. *JAMA* 2010; **303:** 2051–57.

32 Djelantik IG, Gessner BD, Sutanto A, et al. Case fatality proportions and predictive factors for mortality among children hospitalized with severe pneumonia in a rural developing country setting. *J Trop Pediatr* 2003; **49:** 327–32.