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

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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).

See Online for appendix

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 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).

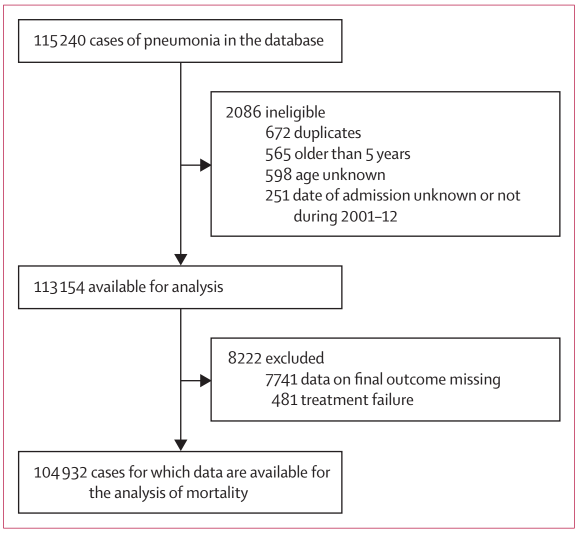

Figure 1: **Study flow diagram**

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.

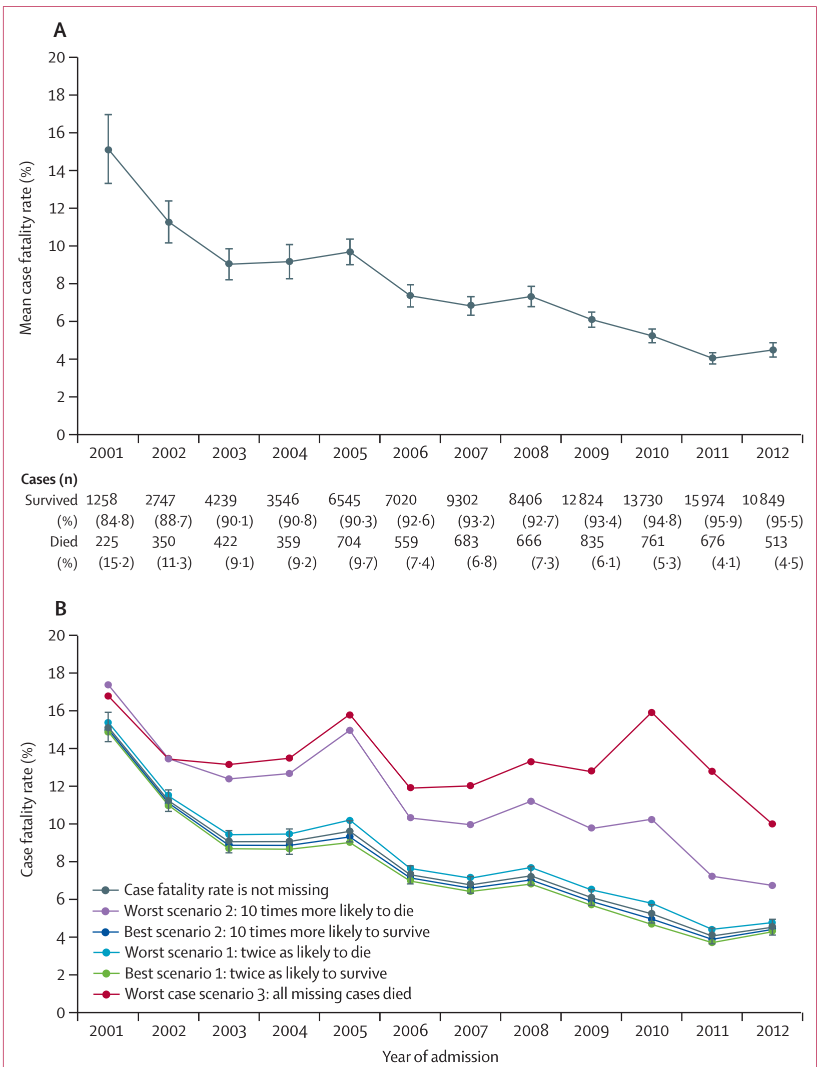

***Figure 2*: (A) Case fatality rate for children with pneumonia in Malawi (missing data not included) and (B) worst and best case scenario case fatality rates on the basis of different assumptions about case fatality for cases with missing data on fatality, 2001–12**
Error bars show 95% CI.

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)	10 506 (75·7%; 74·9–76·4)	11 787 (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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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Lazzerini M, Seward N, Lufesi N, et al. Mortality and its risk factors in Malawian children admitted to hospital with clinical pneumonia, 2001–12: a retrospective observational study. *Lancet Glob Health* 2016; **4:** e57–68.

Supplementary appendix

Mortality and its risk factors in Malawian children hospitalised with clinical pneumonia, 2001 to 2012

Supplementary Figure 1. Yellow form

District Hospital

District Registration No:

PNEUMONIA INPATIENT RECORDING FORM

Name:

Address:

Age (months): Sex (M/F):

Number of days of signs/symptoms: More than 21 days ☐ Less than 21 days ☐

Antibiotic treatment prior to coming to hospital: Yes ☐ No ☐ Self referral ☐ Referred by Health Centre ☐

Date of hospital admission:

Weight Kg Temperature ^{0}C Respiratory rate x 1 minute

Chest Xray Yes ☐ No ☐
If yes date taken and results:

Previous pneumonia in the last 12 months Yes☐ No ☐

Previous hospital admissions for pneumonia in last 12 months Yes☐ No ☐

Clinical features		Classification	Treatment								
CHILD 2 MONTHS TO 5 YEARS			Antibiotic	Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Chest in-drawing	Yes ☐ No ☐	Very severe pneumonia ☐	Benzylpenicillin		| | |	| | |	| | |	| | |	| | |	| | |	| | |
Severe respiratory distress	Yes ☐ No ☐	Severe pneumonia ☐	Amoxycillin		| |	| |	| |	| |	| |	| |	| |
Central cyanosis	Yes ☐ No ☐		Chloramphenicol		| |	| |	| |	| |	| |	| |	| |
Sleepy/difficult to wake	Yes ☐ No ☐	Pneumonia ☐	Cotrimoxazole		|	|	|	|	|	|	|
Convulsions	Yes ☐ No ☐	PCP ☐	Other antibiotic (specify)								
able to breastfeed well	Yes ☐ No ☐		Other treatment								
able to drink	Yes ☐ No ☐	Other (specify) ☐									
Stridor	Yes ☐ No ☐										
Wheeze	Yes ☐ No ☐										
YOUNG INFANT < 2 MONTHS			Antibiotics	Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
		Very severe pneumonia/disease ☐	Gentamicin								
Severe chest in-drawing	Yes ☐ No ☐		Benzylpenicillin		| | |	| | |	| | |	| | |	| | |	| | |	| | |
Central cyanosis	Yes ☐ No ☐	Severe pneumonia ☐	Amoxycillin		| |	| |	| |	| |	| |	| |	| |
Sleepy/difficult to wake	Yes ☐ No ☐	PCP ☐	Other antibiotic (specify)								
Able breastfeed well	Yes ☐ No ☐	Other (specify) ☐									
Wheeze	Yes ☐ No ☐		Other treatment								
Grunting intermittent	Yes ☐ No ☐										
Grunting continuous	Yes ☐ No ☐										
Nasal flaring	Yes ☐ No ☐										
Apnoeic spells	Yes ☐ No ☐										
Convulsions											
HIV status	Positive ☐	Negative ☐	Unknown ☐	Measles at this visit or in past 2 months	Yes ☐ No ☐						
Blood film (malaria)	Positive ☐	Negative ☐	Unknown ☐	Severe malnutrition * (see below)	Yes ☐ No ☐						

Hospitalisation

Duration of hospitalisation in either	______ Hours		______ Days
Admission diagnosis	______	Discharge diagnosis	______

Discharge and Follow-up

Course of antibiotics to be completed at home	Yes ☐	No ☐	Child returned for follow-up visit	Yes ☐	No ☐
Mother informed to return with child once antibiotics completed	Yes ☐	No ☐	Course of antibiotic completed**	Yes ☐	No ☐
			Child fully recovered**	Yes ☐	No ☐

Treatment Results

Treatment completed(1)	☐	Failure at 48 hrs (2)	☐	Failure at Day 5	☐
Left against advise(3)	☐	Transferred (4)	☐	Outcome unknown (5)	☐
Died within 24 hours of admission	☐	Died after 24 hours of admission	☐	**(See below for definitions)**	

Additional Remarks:

______

______

______

Rationale for Information/Recording System

When the decision is reached that the child has pneumonia and requires hospitalisation then the ***"Pneumonia Inpatient Recording Form"*** must be completed in addition to other forms that may be used, such as critical care pathways. The use of this form is a prerequisite of the Project providing the drugs for treatment of such cases. The form is initiated when the patient is started on treatment and is completed on discharge. The form is provided to assist the health worker in providing good quality care for the patient. All information is transferred to the ***Pneumonia Inpatient Register.***

* If NO then tick Outcome Unknown (5) in Treatment Results section

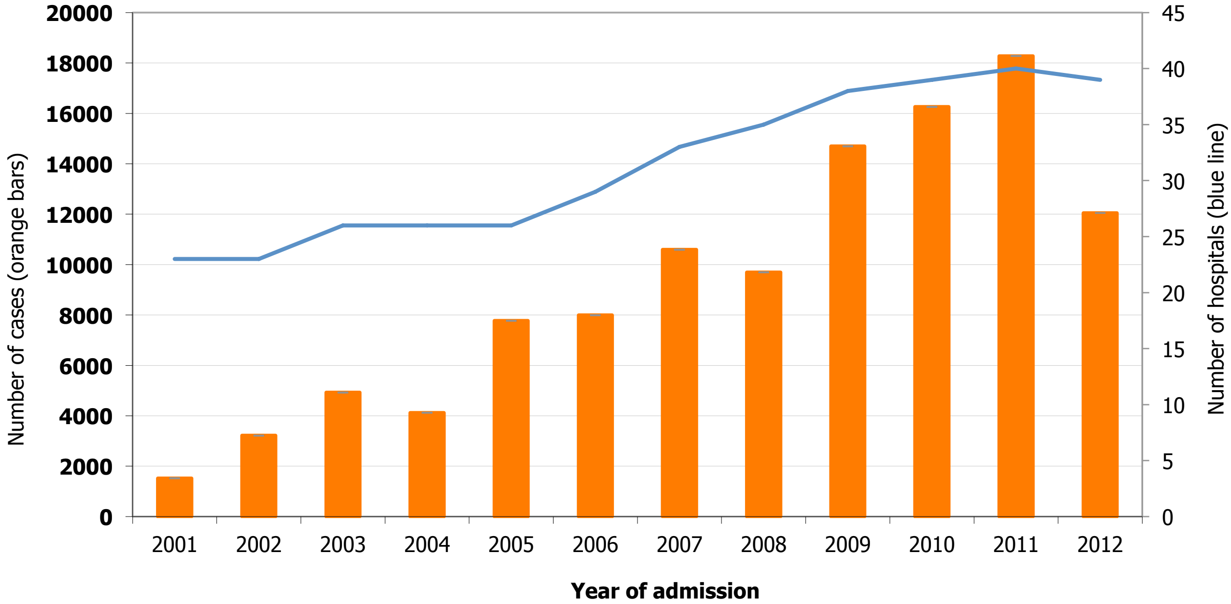
** If YES then child can be registered as Treatment Completed(1) in Treatment Results section

1. Course of antibiotics completed and child fully recovered
2. Treatment failure means: Worsening of fast breathing, or Worsening of chest in-drawing, or Development/persistence of abnormal sleepiness or difficulty in awakening, or development/persistence of inability to drink or poor breastfeeding.
3. Child removed from the hospital against medical advise before treatment is completed
4. Child is referred for treatment to another health facility and the result of treatment is unknown; where the result is known, that result should be recorded in place of the result "transferred
5. When mother does not return with child for follow-up visit once course of antibiotic(s) is finished

Supplementary Figure 2. Map of Malawi showing location of different hospitals enrolled in the study

Abbreviations: CHAM= Christian Health Association of Malawi hospital

Supplementary Figure 3. Number of cases enrolled over time

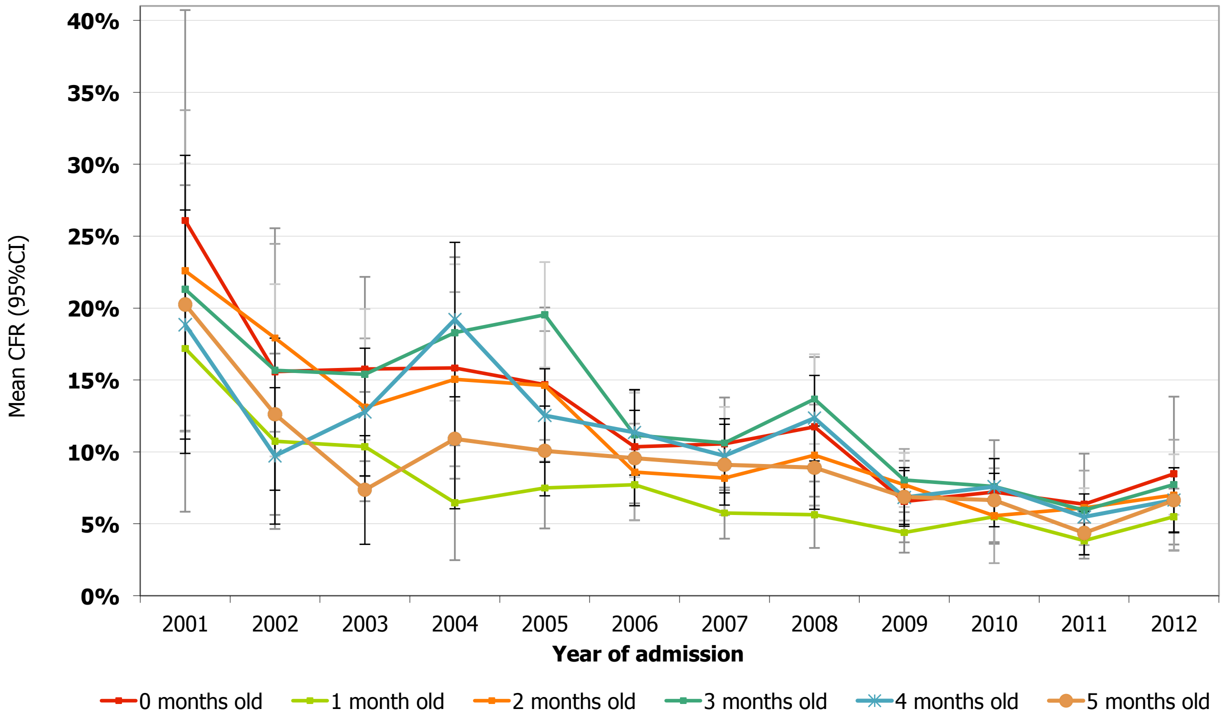


Note: The number of hospitals implementing the Yellow Form increased progressively during time from 2000 to 2011. Only 209 forms were collected from the year 2000 and these are not shown on the graph or included in the analyses in this study. Collection of Yellow forms from hospitals started in early November 2012 and therefore some hospitals did not provided data from the whole of 2012. Data collection ended in March 2013 and therefore very few forms were collected for year 2013 (data not shown).

Supplementary Table 1. Number of cases by region and by type of facility

Region	Type of hospital			
	District	Central	Mission	Total
North (%)	16052 (76.6)	2574 (12.3)	2321 (11.1)	**20947 (18.5)**
Central (%)	35892 (73.6)	5826 (11.9)	7063 (14.5)	**48781 (43.1)**
South (%)	37270 (85.9)	1799 (4.1)	4346 (10.0)	**43415 (38.4)**
Total (%)	**89214 (78.9)**	**10199 (9.0)**	**13730 (12.1)**	**113394 (100)**

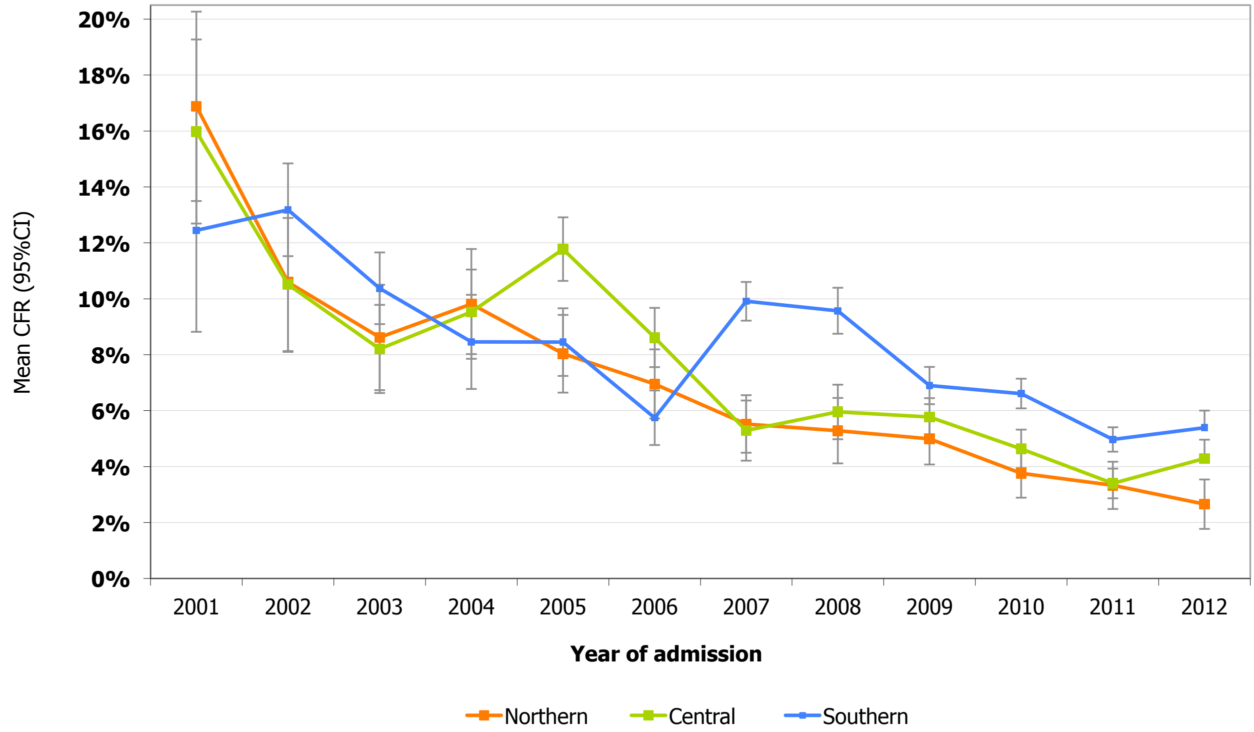
Supplementary Figure 4. Case fatality rate over time by age for each of the first six months



CFR= Case Fatality Rate

Months old	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
0	Survived (%)	34 (73.9)	65 (84.4)	139 (84.2)	101 (84.2)	186 (85.3)	277 (89.6)	398 (89.4)	203 (88.3)	385 (93.4)	270 (92.8)	265 (93.6)	151 (91.5)
	Died (%)	12 (26.1)	12 (15.6)	26 (15.8)	19 (15.8)	32 (14.7)	32 (10.4)	47 (10.6)	27 (11.7)	27 (6.6)	21 (7.2)	18 (6.4)	14 (8.5)
1	Survived (%)	53 (82.8)	133 (89.3)	294 (89.6)	217 (93.5)	420 (92.5)	538 (92.3)	804 (94.3)	503 (94.4)	1021 (95.6)	791 (94.5)	1157 (96.2)	670 (94.5)
	Died (%)	11 (17.2)	16 (10.7)	34 (10.4)	15 (6.5)	34 (7.5)	45 (7.7)	49 (5.7)	30 (5.6)	47 (4.4)	46 (5.5)	46 (3.8)	39 (5.5)
2	Survived (%)	48 (77.4)	87 (82.1)	199 (86.9)	158 (84.9)	333 (85.4)	372 (91.4)	595 (91.8)	443 (90.2)	813 (92.3)	730 (94.4)	1014 (93.9)	624 (93.0)
	Died (%)	14 (22.6)	19 (17.9)	30 (13.1)	28 (15.1)	57 (14.6)	35 (8.6)	53 (8.2)	48 (9.8)	68 (7.7)	43 (5.6)	66 (6.1)	47 (7.0)
3	Survived (%)	85 (78.7)	156 (84.3)	253 (84.6)	250 (81.7)	412 (80.5)	485 (88.8)	631 (89.4)	480 (86.3)	903 (92.0)	803 (92.4)	1075 (94.1)	716 (92.3)
	Died (%)	23 (21.3)	29 (15.7)	46 (15.4)	56 (18.3)	100 (19.5)	61 (11.2)	75 (10.6)	76 (13.7)	79 (8.0)	66 (7.6)	68 (5.9)	60 (7.7)
4	Survived (%)	99 (81.1)	195 (90.3)	246 (87.2)	202 (80.8)	426 (87.5)	476 (88.6)	566 (90.3)	497 (87.7)	818 (93.2)	805 (92.4)	948 (94.5)	588 (93.3)
	Died (%)	23 (18.9)	21 (9.7)	36 (12.8)	48 (19.2)	61 (12.5)	61 (11.4)	61 (9.7)	70 (12.3)	60 (6.8)	66 (7.6)	55 (5.5)	42 (6.7)
5	Survived (%)	63 (79.7)	180 (87.4)	252 (92.6)	196 (89.1)	411 (89.9)	359 (90.4)	469 (90.9)	440 (91.1)	705 (93.1)	814 (93.3)	899 (95.6)	577 (93.4)
	Died (%)	16 (20.3)	26 (12.6)	20 (7.4)	24 (10.9)	46 (10.1)	38 (9.6)	47 (9.1)	43 (8.9)	52 (6.9)	58 (6.7)	41 (4.4)	41 (6.6)

Supplementary Figure 5. Case fatality rate over time by region

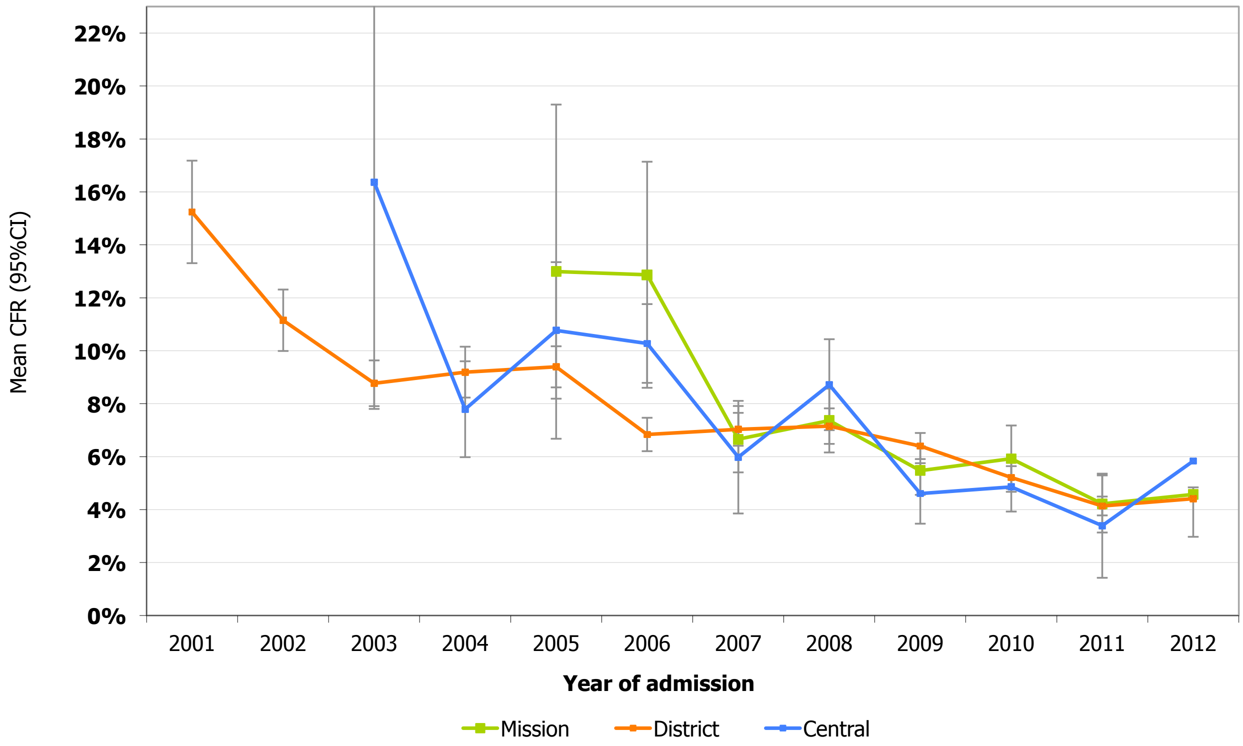


CFR= Case Fatality Rate

Region	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Northern	Survived (%)	453 (83.1)	633 (89.4)	933 (91.4)	937 (90.2)	1568 (92.0)	1766 (93.1)	2104 (94.5)	1613 (94.7)	2417 (95.0)	2150 (96.2)	2090 (96.7)	1649 (97.3)
	Died (%)	92 (16.9)	75 (10.6)	88 (8.6)	102 (9.8)	137 (8.0)	132 (7.0)	123 (5.5)	90 (5.3)	127 (5.0)	84 (3.8)	72 (3.3)	45 (2.7)
Central	Survived (%)	389 (84.0)	1337 (89.5)	1846 (91.8)	1224 (90.5)	2615 (88.2)	3203 (91.4)	4280 (94.7)	3364 (94.1)	4899 (94.2)	6422 (95.4)	7135 (96.6)	4618 (95.7)
	Died (%)	74 (16.0)	157 (10.5)	165 (8.2)	129 (9.5)	349 (11.8)	302 (8.6)	239 (5.3)	213 (6.0)	300 (5.8)	312 (4.6)	251 (3.4)	207 (4.3)
Southern	Survived (%)	415 (87.6)	777 (86.8)	1460 (89.6)	1385 (91.5)	2361 (91.5)	2051 (94.3)	2918 (90.1)	3429 (90.4)	5507 (93.1)	5156 (93.4)	6748 (95.0)	4579 (94.6)
	Died (%)	59 (12.5)	118 (13.2)	169 (10.4)	128 (8.5)	218 (8.5)	125 (5.7)	321 (9.9)	363 (9.6)	408 (6.9)	365 (6.6)	353 (5.0)	261 (5.4)

For all geographical regions, the CFR was significantly higher in 2001 compared to 2012 (Supplementary Figure 5): Southern Malawi (12.4%, CI 9.8% to 15.7% vs. 5.4%, CI 4.8% to 6.1%; $p < 0.001$); Central Malawi (16.0%, CI 12.9% to 19.6% vs. 4.3%, CI 3.8% to 4.9%; $p < 0.001$); Northern Malawi (16.9%, CI 14.0% to 20.2% vs. 2.7%, CI 2.0% to 3.5%; $p < 0.001$). There were some significant differences in CFR between regions over time, with Southern Malawi showing from year 2007 a significantly higher CFR compared to Northern and Central Malawi (Supplementary Figure 5).

Supplementary Figure 6. Case fatality rate over time by type of hospital



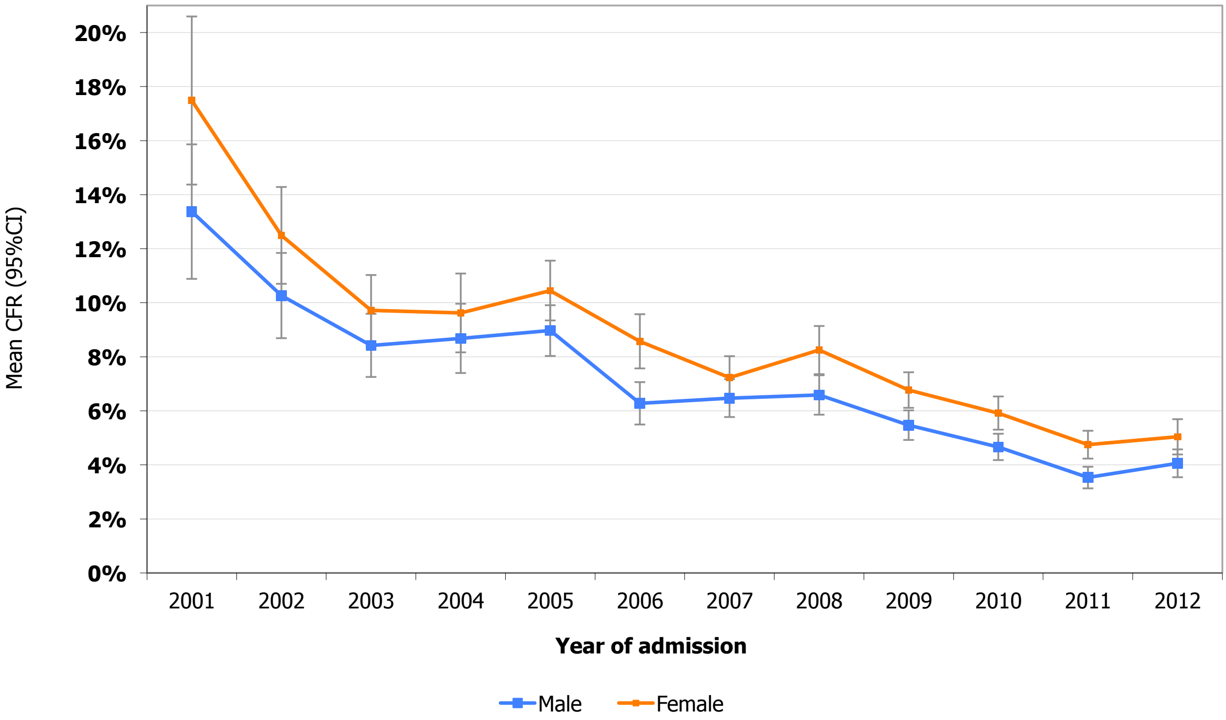
CFR= Case Fatality Rate

Note: Large confidence intervals for CFRs of Mission and Central hospitals during year 2003 to 2006 are explained by the small number of hospitals enrolled at that time, and a relative low number of events. The scaling up of data collection through the Yellow Form started with district hospitals in 2001, and progressively enclosed Central Hospitals in year 2003, and CHAM hospitals from year 2005.

Hosp.	**Cases (n)**	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Mission	Survived (%)	14 (87.5)	4 (50.0)	3 (75.0)	17 (85.0)	134 (87.0)	264 (87.1)	1668 (93.3)	1925 (92.6)	2590 (94.5)	1540 (94.1)	1591 (95.8)	834 (95.4)
	Died (%)	2 (12.5)	4 (50.0)	1 (25.0)	3 (15.0)	20 (13.0)	39 (12.9)	119 (6.7)	153 (7.4)	150 (5.5)	97 (5.9)	70 (4.2)	40 (4.6)
District	Survived (%)	1240 (84.8)	2741 (88.9)	4098 (91.2)	3458 (90.8)	5258 (90.6)	6171 (93.2)	6502 (93.0)	5727 (92.9)	9488 (93.6)	10600 (94.8)	12588 (95.9)	9334 (95.6)
	Died (%)	223 (15.2)	344 (11.2)	394 (8.8)	350 (9.2)	545 (9.4)	453 (6.8)	492 (7.0)	441 (7.1)	649 (6.4)	583 (5.2)	543 (4.1)	431 (4.4)
Central	Survived (%)	3 (100)	2 (50.0)	138 (83.6)	71 (92.2)	1152 (89.2)	585 (89.7)	1132 (94.0)	754 (91.3)	745 (95.4)	1588 (95.1)	1794 (96.6)	678 (94.2)
	Died (%)	0 (0)	2 (50.0)	27 (16.4)	6 (7.8)	139 (10.8)	67 (10.3)	72 (6.0)	72 (8.7)	36 (4.6)	81 (4.9)	63 (3.4)	42 (5.8)

All healthcare facility types showed a significant decrease in CFRs (Supplementary Figure 6): district hospitals (15.2%, CI 13.5% to 17.2% in 2001 vs. 4.4%, CI 4.0% to 4.8% in 2012; p< 0.001); central hospitals (16.4%, CI 11.5% to 22.8% in 2003 vs. 5.8%, CI 4.3% to 7.8% in 2012; p< 0.001); mission hospital (13.0%, CI 8.5% to 19.3% in 2005 vs. 4.6%, CI 3.4% to 6.2% in 2012; p< 0.001).

Supplementary Figure 7. Case fatality rate over time by sex

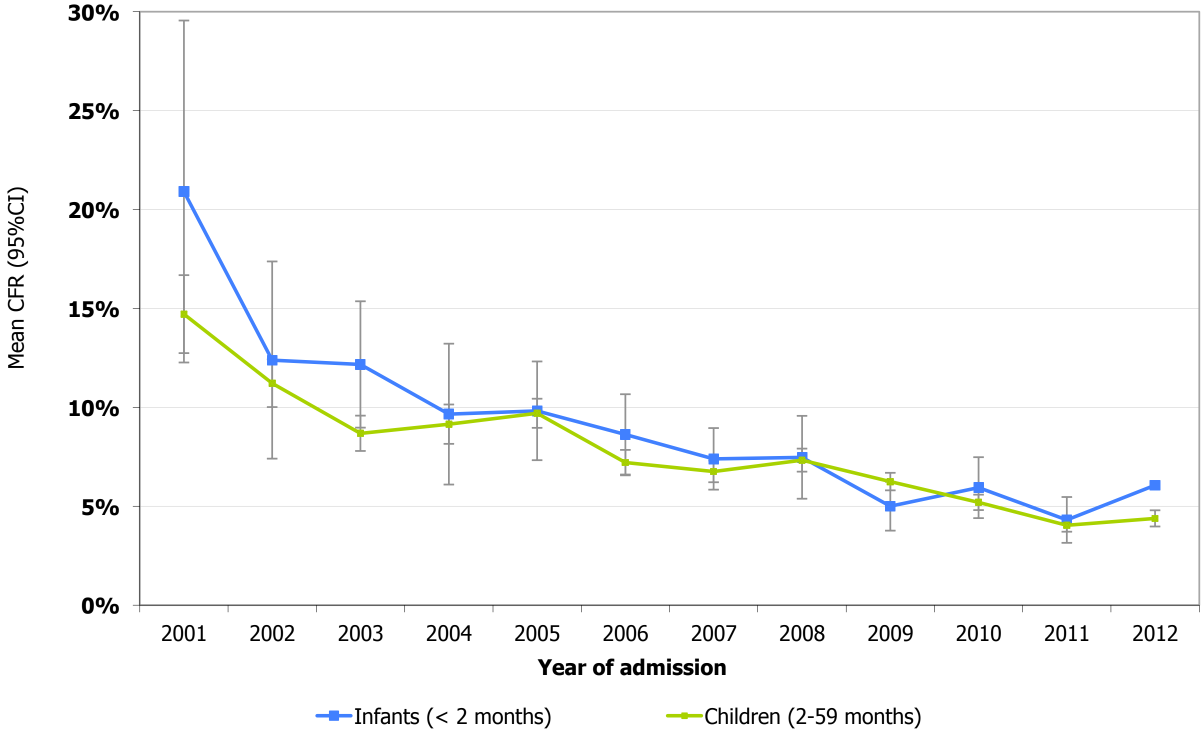


CFR= Case Fatality Rate

Sex	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Male	Survived (%)	719 (86.6)	1451 (89.7)	2240 (91.6)	1914 (91.3)	3542 (91.0)	3852 (93.7)	4872 (93.5)	4582 (93.4)	6862 (94.5)	7586 (95.3)	8743 (96.5)	6029 (95.9)
	Died (%)	111 (13.4)	166 (10.3)	206 (8.4)	182 (8.7)	349 (9.0)	258 (6.3)	337 (6.5)	323 (6.6)	397 (5.5)	371 (4.7)	320 (3.5)	255 (4.1)
Female	Survived (%)	538 (82.5)	1282 (87.5)	1979 (90.3)	1606 (90.4)	2879 (89.5)	3029 (91.4)	4186 (92.8)	3671 (91.8)	5661 (93.2)	5821 (94.1)	6845 (95.3)	4599 (95.0)
	Died (%)	114 (17.5)	183 (12.5)	213 (9.7)	171 (9.6)	336 (10.5)	284 (8.6)	326 (7.2)	330 (8.2)	411 (6.8)	366 (5.9)	341 (4.7)	244 (5.0)

The CFR significantly decreased during the period 2001 to 2012 for both females (17.5%, CI 14.8% to 20.6% vs. 5.0%, CI 4.5% to 5.7%; p< 0.001) and males (13.4%, CI 11.2% to 15.9% vs. 4.1%, CI 3.6% to 4.6%; p< 0.001; Supplementary Figure 7). Overall mortality was significantly higher in females compared to males (3400/46138 (7.4%) vs. 3333/56570 (5.9%), OR 1.27, CI 1.21 to 1.34) and a significant difference in CFRs by sex category was found in most of the study years.

Supplementary Figure 8. Case fatality rate over time by age classes

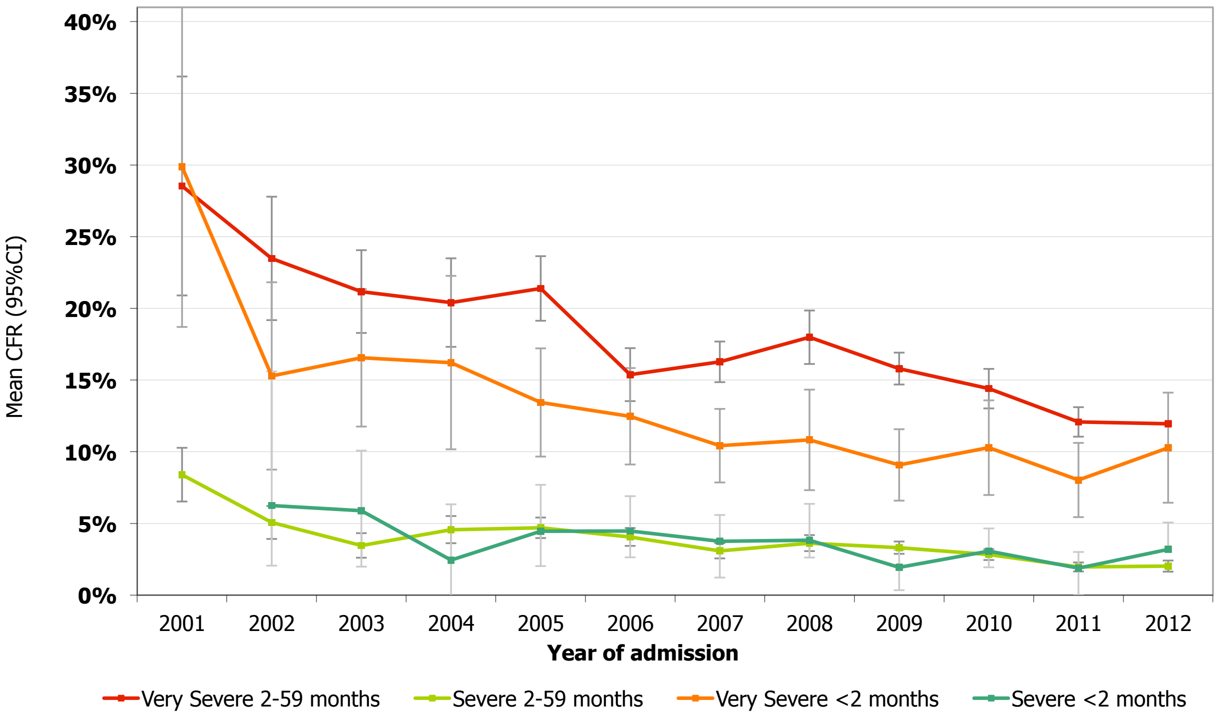


CFR= Case Fatality Rate

Age	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
<2 mo	Survived (%)	87 (79.1)	198 (87.6)	433 (87.8)	318 (90.3)	606 (90.2)	815 (91.4)	1202 (92.6)	706 (92.5)	1406 (95.0)	1061 (94.1)	1422 (95.7)	821 (93.9)
	Died (%)	23 (20.9)	28 (12.4)	60 (12.2)	34 (9.7)	66 (9.8)	77 (8.6)	96 (7.4)	57 (7.5)	74 (5.0)	67 (5.9)	64 (4.3)	53 (6.1)
2-59 mo	Survived (%)	1171 (85.3)	2549 (88.8)	3806 (91.3)	3228 (90.9)	5939 (90.3)	6205 (92.8)	8100 (93.2)	7700 (92.7)	11418 (93.8)	12669 (94.8)	14552 (96.0)	10028 (95.6)
	Died (%)	202 (14.7)	322 (11.2)	362 (8.7)	325 (9.1)	638 (9.7)	482 (7.2)	587 (6.8)	609 (7.3)	761 (6.2)	694 (5.2)	612 (4.0)	460 (4.4)

The CFR significantly decreased during the period 2001 to 2012 in both young infants <2 months (20.9%, CI 14.3% to 29.6% vs. 6.1%, CI 4.7% to 7.9%; p< 0.001; Supplementary Figure 8) and children 2-59 months (14.7%, CI 12.9% to 16.7% vs. 4.4%, CI 4.0% to 4.8%; p< 0.001). Overall, mortality was significantly higher in young infants than in children (712/9959 (7.2%) vs. 6191/94973 (6.5%), OR 1.10, CI 1.02 to 1.20), although when results were compared by study year, there was a statistically significant difference in annual CFR only in 2003 and 2012.

Supplementary Figure 9. Case fatality rate over time by severity of pneumonia

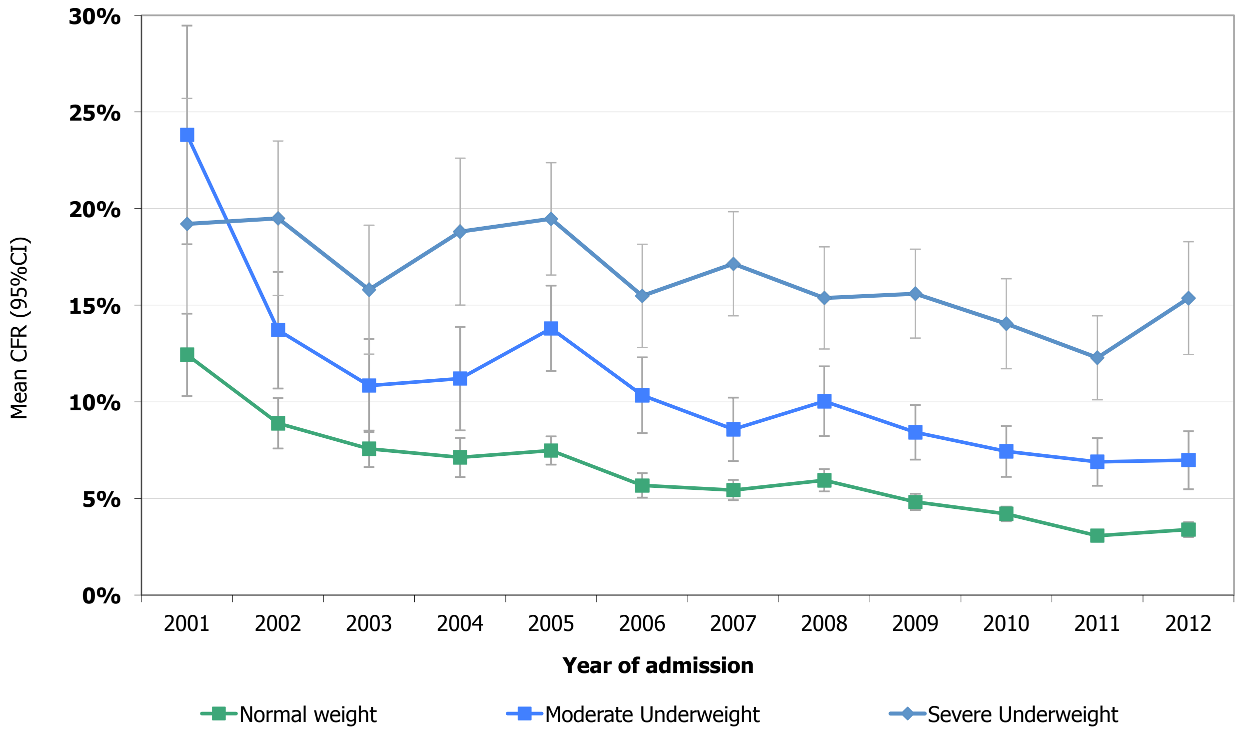


CFR= Case Fatality Rate

Severity	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Very Severe 2-59 mo	Survived (%)	303 (71.5)	730 (76.5)	957 (78.8)	796 (79.6)	1478 (78.6)	1508 (84.6)	1909 (83.7)	1737 (82.0)	2399 (84.2)	2276 (85.6)	2679 (87.9)	2129 (88.1)
	Died (%)	121 (28.5)	224 (23.5)	257 (21.2)	204 (20.4)	402 (21.4)	274 (15.4)	371 (16.3)	381 (18.0)	450 (15.8)	383 (14.4)	368 (12.1)	289 (11.9)
Severe 2-59 mo	Survived (%)	807 (91.6)	1705 (94.9)	2704 (96.5)	2343 (95.4)	4264 (95.3)	4520 (95.9)	5870 (96.9)	5685 (96.4)	8703 (96.7)	10044 (97.2)	11491 (98.0)	7687 (98.0)
	Died (%)	74 (8.4)	91 (5.1)	97 (3.5)	112 (4.6)	210 (4.7)	191 (4.1)	187 (3.1)	214 (3.6)	298 (3.3)	292 (2.8)	230 (2.0)	159 (2.0)
Very Severe <2 mo	Survived (%)	54 (70.1)	133 (84.7)	237 (83.5)	155 (83.8)	335 (86.6)	400 (87.5)	593 (89.6)	346 (89.2)	581 (90.9)	375 (89.7)	504 (92.0)	288 (89.7)
	Died (%)	23 (29.9)	24 (15.3)	47 (16.5)	30 (16.2)	52 (13.4)	57 (12.5)	69 (10.4)	42 (10.8)	58 (9.1)	43 (10.3)	44 (8.0)	33 (10.3)
Severe <2 mo	Survived (%)	32 (100)	60 (93.8)	192 (94.1)	160 (97.6)	257 (95.5)	406 (95.5)	589 (96.2)	352 (96.2)	810 (98.1)	664 (96.9)	887 (98.1)	516 (96.8)
	Died (%)	0 (0)	4 (6.3)	12 (5.9)	4 (2.4)	12 (4.5)	19 (4.5)	23 (3.8)	14 (3.8)	16 (1.9)	21 (3.1)	17 (1.9)	17 (3.2)

Over time there was a significant decrease in CFR both for cases of very severe pneumonia in children aged 2-59 months (28.5%, CI 24.4% to 33.0% vs. 12.0%, CI 10.7% to 13.3% vs.; p< 0.001), severe pneumonia in children aged 2-59 months (8.4%, CI 6.7% to 10.4% vs. 2.0%, CI 1.7% to 2.4%; p< 0.001), and very severe pneumonia in young infants <2 months (29.9%, CI 20.7% to 41.0% vs. 10.3%, CI 7.4% to 14.1%; p< 0.001; Supplementary Figure 9). There was less of a decrease over time in CFR for severe pneumonia in young infants <2 months (6.3%, CI 2.3% to 15.6% in 2002 vs. 3.2%, CI 2.0% to 5.1% in 2012; p= 0.02). Overall mortality was significantly higher for very severe pneumonia compared to severe pneumonia both in children (3804/22990 (16.6%) vs. 2206/69078 (3.2%) OR 6.01, CI 5.69 to 6.35) and in young infants (528/4610 (11.5%) vs. 165/5175 (3.2%) OR 3.93, CI 3.28 to 4.70), and such difference was appreciable throughout the whole study period (Supplementary Figure 9).

Supplementary Figure 10. Case fatality rate over time in children with normal weight and in underweight children



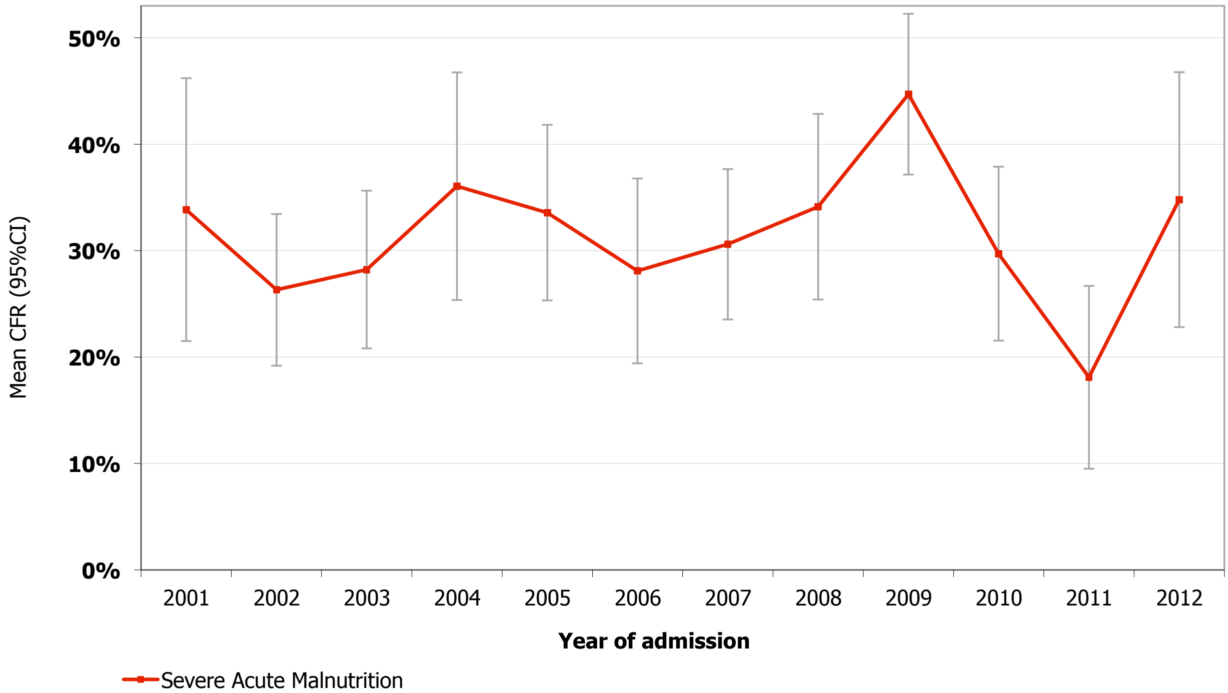
CFR= Case Fatality Rate

Note: moderate underweight was defined as weight-for-age <-2 standard deviation (SD) from the mean based on the WHO 2006 growth reference standards;[1] severe underweight was defined as weight-for-age <-3 SD based on the WHO 2006 growth reference standards.[1]

Weight	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Normal	Survived (%)	923 (87.6)	1886 (91.1)	3103 (92.4)	2595 (92.9)	4996 (92.5)	5372 (94.3)	7396 (94.6)	6606 (94.1)	10354 (95.2)	11260 (95.8)	13331 (96.9)	9049 (96.6)
	Died (%)	131 (12.4)	184 (8.9)	254 (7.6)	199 (7.1)	404 (7.5)	323 (5.7)	425 (5.4)	417 (5.9)	524 (4.8)	493 (4.2)	422 (3.1)	317 (3.4)
Moderate Under-weight	Survived (%)	192 (76.2)	510 (86.3)	683 (89.2)	571 (88.8)	912 (86.2)	971 (89.7)	1205 (91.4)	1112 (90.0)	1566 (91.6)	1631 (92.6)	1757 (93.1)	1227 (93.0)
	Died (%)	60 (23.8)	81 (13.7)	83 (10.8)	72 (11.2)	146 (13.8)	112 (10.3)	113 (8.6)	124 (10.0)	144 (8.4)	131 (7.4)	130 (6.9)	92 (7.0)
Severe Under-weight	Survived (%)	143 (80.8)	351 (80.5)	453 (84.2)	380 (81.2)	637 (80.5)	677 (84.5)	701 (82.9)	688 (84.6)	904 (84.4)	839 (86.0)	886 (87.7)	573 (84.6)
	Died (%)	34 (19.2)	85 (19.5)	85 (15.8)	88 (18.8)	154 (19.5)	124 (15.5)	145 (17.1)	125 (15.4)	167 (15.6)	137 (14.0)	124 (12.3)	104 (15.4)

When CFR was stratified by nutritional status a significant decrease in CFR from year 2001 to 2012 was observed in WHO-defined well-nourished children (12.4%, CI 10.6% to 14.6% vs. 3.4%, CI 3.0% to 3.8%; p< 0.001) and in children moderately underweight per WHO criteria (23.8%, CI 18.9% to 29.5% vs. 7.0%, CI 5.7% to 8.5%, p< 0.001; Supplementary Figure 10). In children severely underweight by WHO standards and with NCHS-defined severe acute malnutrition mortality did not significantly change over time (Supplementary Figures 10 and 11). Compared to well-nourished children, CFR were significantly higher for children WHO moderately underweight (3237/75746 (4.3%) vs. 1315/13824 (9.5%), OR 2.35, CI 2.20 to 2.52) and WHO severely underweight (1396/8741 (16.0%), OR 4.26, CI 3.98 to 4.55). Children with NCHS-defined severe acute malnutrition also had significantly higher CFR (488/1556 (31.4%) than those without (5227/87689 (6.0%), OR 7.21, CI 6.45 to 8.05). A significant difference in CFR by children with different nutritional status was appreciable in each year of the study.

Supplementary Figure 11. Case fatality rate over time in children with severe acute malnutrition

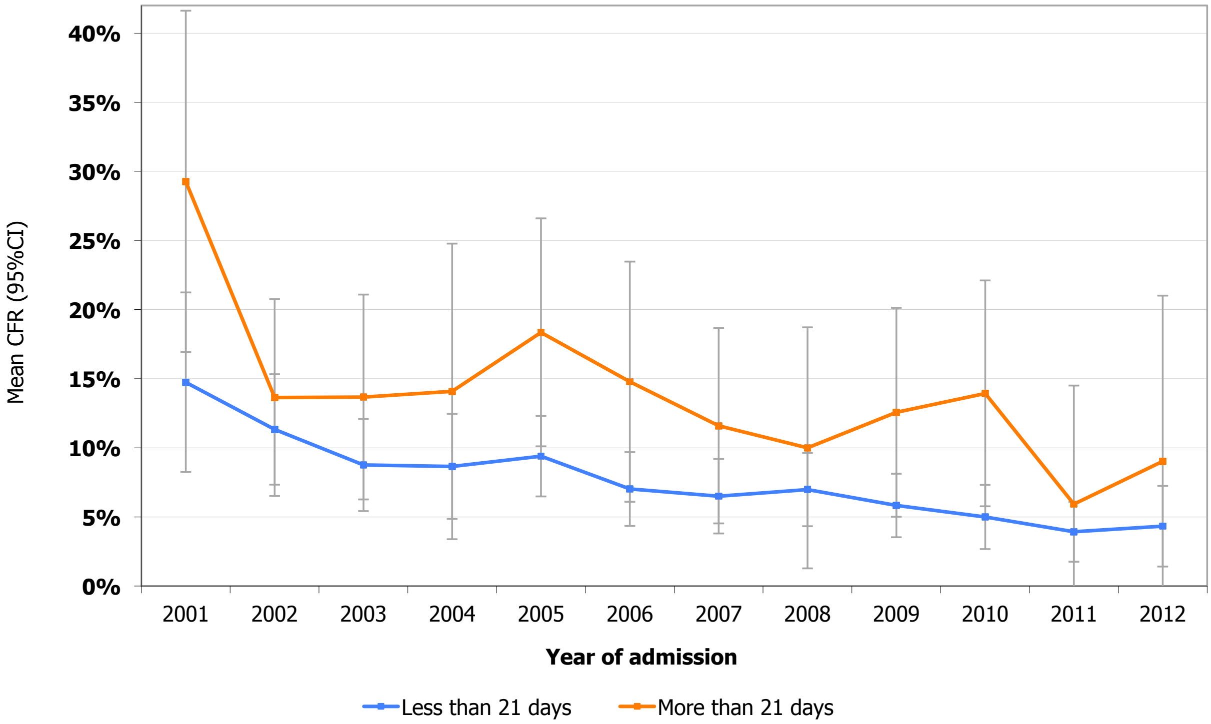


CFR= Case Fatality Rate

Note: The diagnosis of severe acute malnutrition was made prospectively during patient care by the health worker per the National Centre for Health Statistics (NCHS) criteria used for standard clinical care in Malawi.[12, 13]

	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Severe Acute Malnutr.	Survived (%)	43 (66.2)	126 (73.7)	117 (71.8)	55 (64.0)	93 (66.4)	87 (71.9)	127 (69.4)	83 (65.9)	94 (55.3)	97 (70.3)	86 (81.9)	45 (65.2)
	Died (%)	22 (33.8)	45 (26.3)	46 (28.2)	31 (36.0)	47 (33.6)	34 (28.1)	56 (30.6)	43 (34.1)	76 (44.7)	41 (29.7)	19 (18.1)	24 (34.8)

Supplementary Figure 12. Case fatality rate over time by duration of the disease

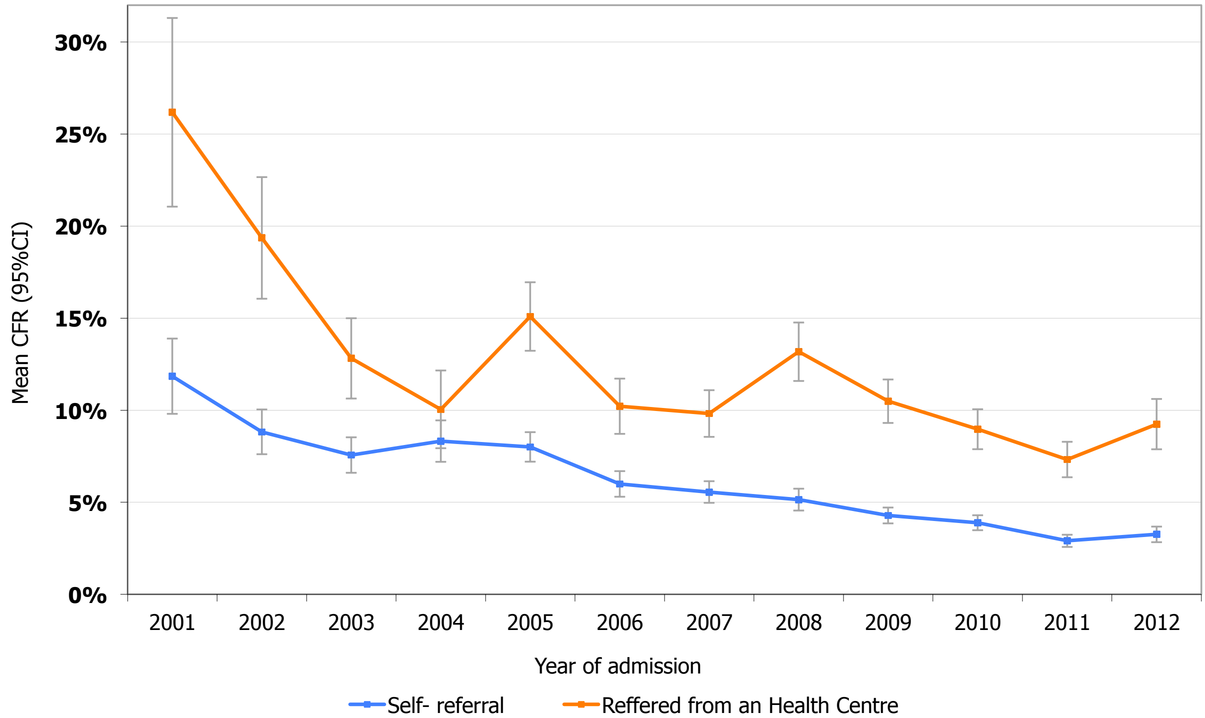


CFR= Case Fatality Rate

	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
<21 days	Survived (%)	1203 (85.3)	2607 (88.7)	3897 (91.2)	3188 (91.3)	5788 (90.6)	6318 (93.0)	8207 (93.5)	7552 (93.0)	11626 (94.2)	12261 (95.0)	13993 (96.1)	9545 (95.7)
	Died (%)	208 (14.7)	333 (11.3)	374 (8.8)	302 (8.7)	600 (9.4)	477 (7.0)	570 (6.5)	566 (7.0)	720 (5.8)	645 (5.0)	572 (3.9)	432 (4.3)
>=21 days	Survived (%)	29 (70.7)	57 (86.4)	101 (86.3)	122 (85.9)	218 (81.6)	196 (85.2)	282 (88.4)	279 (90.0)	334 (87.4)	284 (86.1)	270 (94.1)	232 (91.0)
	Died (%)	12 (29.3)	9 (13.6)	16 (13.7)	20 (14.1)	49 (18.4)	34 (14.8)	37 (11.6)	31 (10.0)	48 (12.6)	46 (13.9)	17 (5.9)	23 (9.0)

A significant decrease in CFR from 2001 to 2012 was observed in children hospitalised with symptoms lasting less than 21 days (14.7%, CI 13.0% to 16.7% vs. 4.3%, CI 3.9% to 4.7%; p< 0.001), but not for those with symptoms lasting 21 days or more (Supplementary Figure 12). Overall mortality was significantly higher in children with disease duration >21 days (350/2801 (12.5%) vs. 5897/93134 (6.3%), OR 2.11, CI 1.88 to 2.37).

Supplementary Figure 13. Case fatality rate over time by type of access

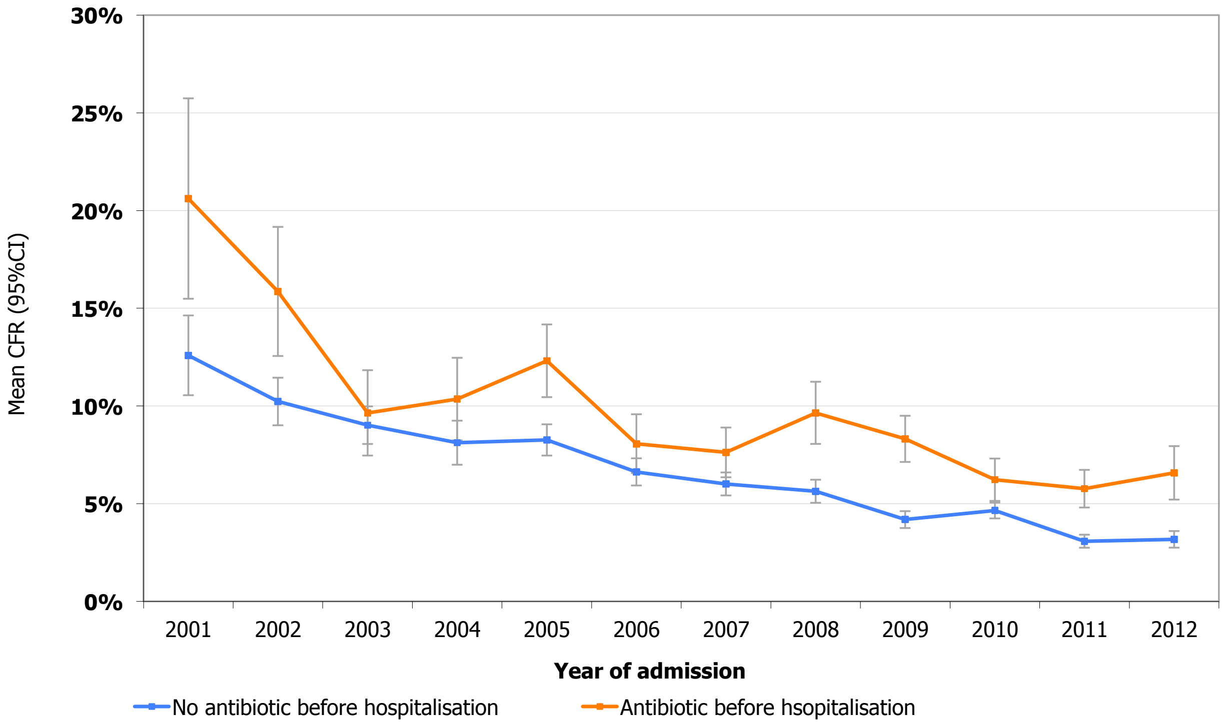


CFR= Case Fatality Rate

	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Self-referral	Survived (%)	975 (88.2)	2139 (91.2)	2981 (92.4)	2379 (91.7)	4436 (92.0)	4639 (94.0)	6056 (94.4)	5608 (94.9)	8800 (95.7)	9088 (96.1)	10528 (97.1)	7339 (96.7)
	Died (%)	131 (11.8)	207 (8.8)	244 (7.6)	216 (8.3)	386 (8.0)	296 (6.0)	356 (5.6)	304 (5.1)	394 (4.3)	368 (3.9)	315 (2.9)	247 (3.3)
Referred From a HC	Survived (%)	234 (73.8)	500 (80.6)	898 (87.2)	833 (90.0)	1328 (84.9)	1582 (89.8)	2112 (90.2)	1667 (86.8)	2534 (89.5)	2690 (91.0)	2924 (92.7)	1777 (90.8)
	Died (%)	83 (26.2)	120 (19.4)	132 (12.8)	93 (10.0)	236 (15.1)	180 (10.2)	230 (9.8)	253 (13.2)	297 (10.5)	265 (9.0)	231 (7.3)	181 (9.2)

For children referred to the hospital by a health centre, CFR was significantly lower in 2012 compared to 2001 (9.2%, CI 8.0% to 10.6% vs. 26.2%, CI 21.6% to 31.3%; p< 0.001), as was CFR for those who were self-referred (2.9%, CI 2.6% to 3.2% vs. 11.8%, CI 10.1% to 13.9%; p< 0.001, Supplementary Figure 13). Mortality was significantly higher in children referred from health centres than from children self-referred, throughout the study period (2329/21668 (10.8%) vs. 3522/69185 (5.1%), OR 2.25, CI 2.13 to 2.37.

Supplementary Figure 14. Case fatality rate over time in children receiving and not receiving antibiotics before the hospitalisation.

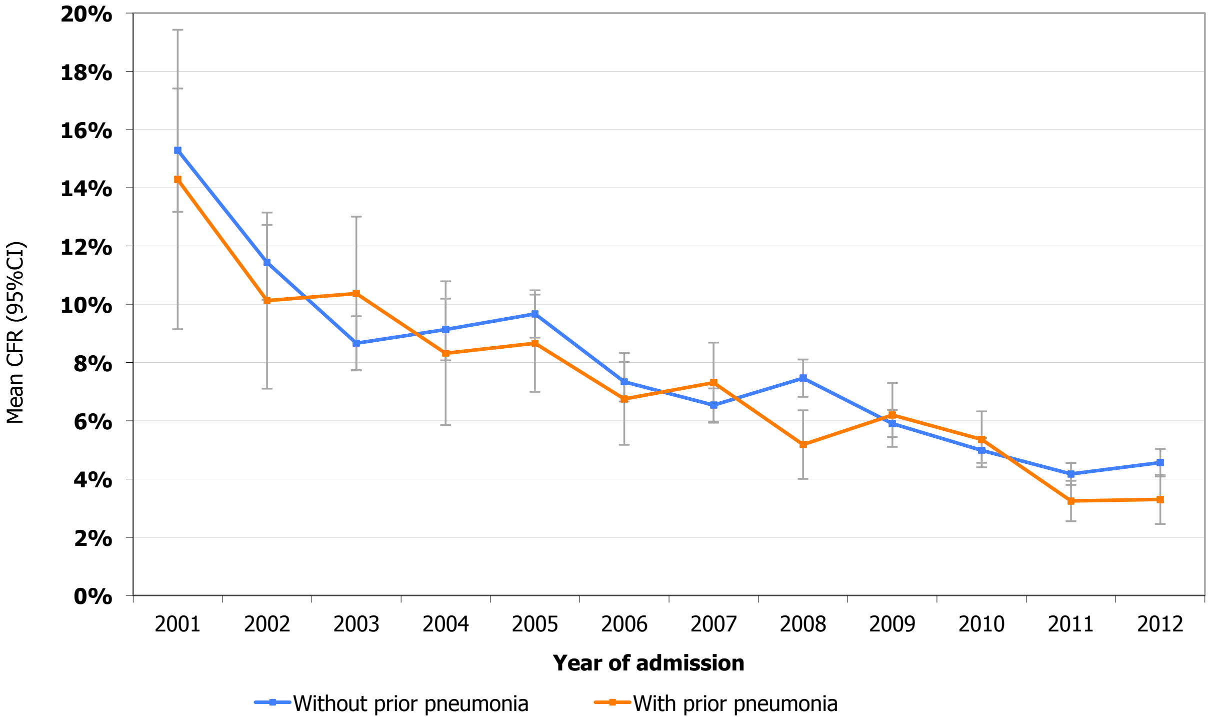


CFR= Case Fatality Rate

	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No prior Antibiotic	Survived (%)	875 (87.4)	1834 (89.8)	2451 (91.0)	1912 (91.9)	3643 (91.7)	3326 (93.4)	4488 (94.0)	4203 (94.4)	6566 (95.8)	6539 (95.3)	7089 (96.9)	5276 (96.8)
	Died (%)	126 (12.6)	209 (10.2)	243 (9.0)	169 (8.1)	328 (8.3)	236 (6.6)	287 (6.0)	251 (5.6)	287 (4.2)	319 (4.7)	225 (3.1)	173 (3.2)
Prior Antibiotic	Survived (%)	285 (79.4)	557 (84.1)	1068 (90.4)	918 (89.6)	1617 (87.7)	2062 (91.9)	2629 (92.4)	2098 (90.4)	3462 (91.7)	3674 (93.8)	4021 (94.2)	2472 (93.4)
	Died (%)	74 (20.6)	105 (15.9)	114 (9.6)	106 (10.4)	227 (12.3)	181 (8.1)	217 (7.6)	224 (9.6)	314 (8.3)	244 (6.2)	246 (5.8)	174 (6.6)

CFRs significantly decreased both in children receiving an antibiotic before hospitalisation (20.6%, CI 16.7% to 25.1% vs. 6.6%, CI 5.7% to 7.6%%; p< 0.001) and in those not receiving it (12.5%, CI 10.7% to 14.8% vs. 3.2%, CI 2.7% to 3.7%; p< 0.001, Supplementary Figure 14), with children receiving antibiotics being associated with an higher odds of death (2255/27385 (8.2%) vs. 2893/51542 (5.6%), OR 1.51, CI 1.43 to 1.60), probably due to initial prescription of antibiotics by community health workers being more likely in more severe cases as per IMCI guidelines.

Supplementary Figure 15. Case fatality rate over time in children with and without an episode of pneumonia in the previous 12 months

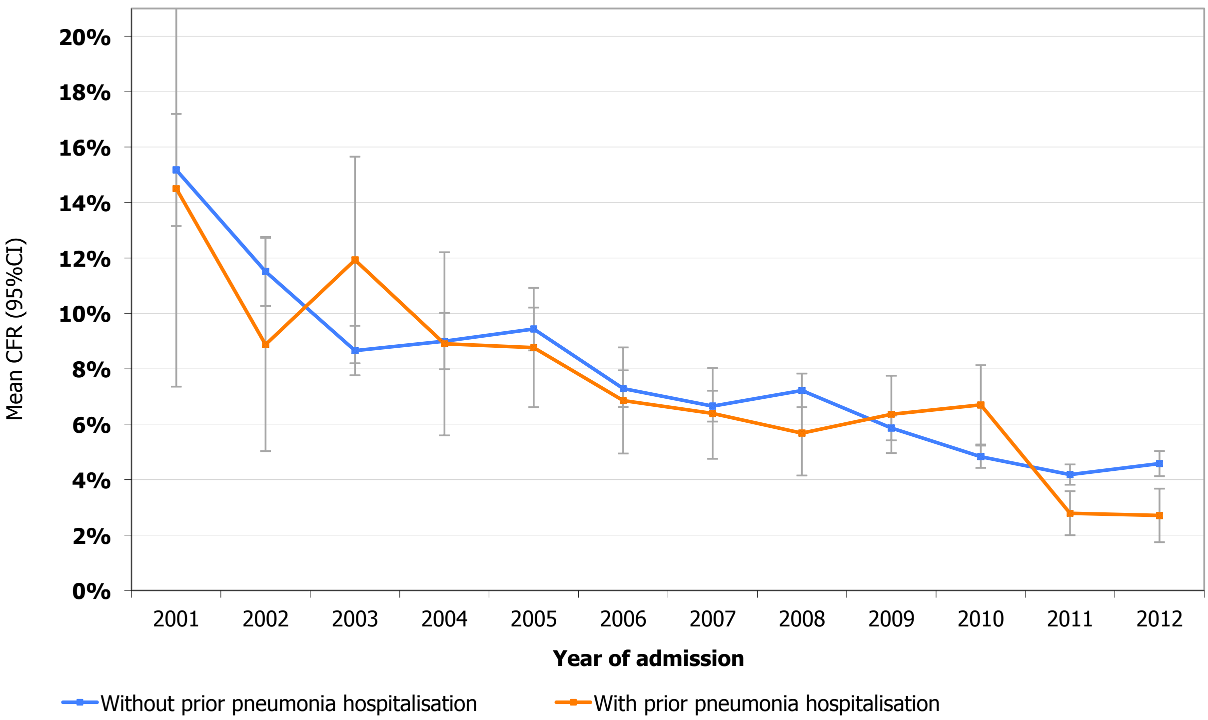


CFR= Case Fatality Rate

	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No prior Pneum.	Survived (%)	1047 (84.7)	2292 (88.6)	3574 (91.3)	2846 (90.1)	4906 (90.3)	5693 (92.7)	7248 (93.5)	6434 (92.5)	10020 (94.1)	10283 (95.0)	11229 (95.8)	7743 (95.4)
	Died (%)	189 (15.3)	296 (11.4)	339 (8.7)	286 (9.1)	525 (9.7)	451 (7.3)	507 (6.5)	519 (7.5)	629 (5.9)	539 (5.0)	489 (4.2)	370 (4.6)
Prior Pneum.	Survived (%)	198 (85.7)	435 (89.9)	562 (89.6)	562 (91.7)	1170 (91.3)	1105 (93.2)	1496 (92.7)	1574 (94.8)	2043 (93.8)	2330 (94.6)	2921 (96.8)	2081 (96.7)
	Died (%)	33 (14.3)	49 (10.1)	65 (10.4)	51 (8.3)	111 (8.7)	80 (6.8)	118 (7.3)	86 (5.2)	135 (6.2)	132 (5.4)	98 (3.2)	71 (3.3)

CFR significantly decreased both in children with or without an episode of pneumonia in the previous 12 months (with pneumonia: CFR 14.3%, CI 10.3% to 19.4% vs. 3.3%, CI 2.6% to 4.1%; p< 0.001; without pneumonia in the previous 12 months: CFR 15.3%, CI 13.4% to 17.4% vs. 4.6%, CI 4.1% to 5.0%, p< 0.001; Supplementary Figure 15), as well as in children with or without a pneumonia hospitalisation in the previous 12 months (with hospitalisation: CFR 14.5% CI 9.4% to 21.7% vs. 2.7% CI 2.0% to 3.7%; p< 0.001; without hospitalisation: CFR 15.2% CI 13.3%. to 17.2% vs. 4.6% CI 4.2% to 5.0%, p< 0.001; Supplementary Figure 16). Overall mortality was significantly lower in children with a previous diagnosis of pneumonia (1040/17744 (5.9%) vs. 5235/79544 (6.6%), OR 0.88, CI 0.83 to 0.95) or with a previous pneumonia hospitalisation (673/11578 (5.8%) vs. 5566/85440 (6.5%), OR 0.89, CI 0.82 to 0.96).

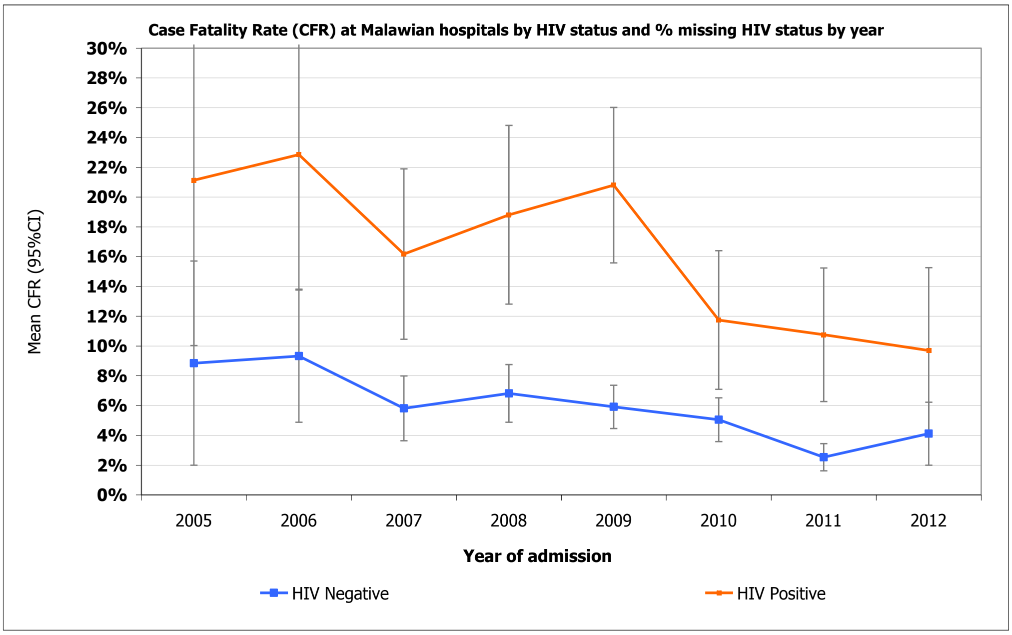
Supplementary Figure 16. Case fatality rate over time in children with and without hospitalisation for pneumonia in the previous 12 months



CFR= Case Fatality Rate

	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No prior Pneum. Hosp.	Survived (%)	1135 (84.8)	2453 (88.5)	3808 (91.3)	3054 (91.0)	5336 (90.6)	5983 (92.7)	7734 (93.3)	6951 (92.8)	10690 (94.1)	11235 (95.2)	12052 (95.8)	8391 (95.4)
	Died (%)	203 (15.2)	319 (11.5)	361 (8.7)	302 (9.0)	556 (9.4)	470 (7.3)	551 (6.7)	541 (7.2)	666 (5.9)	570 (4.8)	526 (4.2)	403 (4.6)
Prior Pneum. Hosp.	Survived (%)	112 (85.5)	267 (91.1)	325 (88.1)	348 (91.1)	739 (91.2)	788 (93.1)	996 (93.6)	1047 (94.3)	1326 (93.6)	1309 (93.3)	2057 (97.2)	1437 (97.3)
	Died (%)	19 (14.5)	26 (8.9)	44 (11.9)	34 (8.9)	71 (8.8)	58 (6.9)	68 (6.4)	63 (5.7)	90 (6.4)	94 (6.7)	59 (2.8)	40 (2.7)

Supplementary Figure 17. Case fatality rate over time by HIV status



CFR= Case Fatality Rate

HIV	Cases (n)	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
HIV negative	Survived (%)	21 (100)	32 (100)	44 (93.6)	36 (92.3)	103 (91.2)	214 (90.7)	567 (94.2)	766 (93.2)	1178 (94.1)	1034 (94.9)	1502 (97.5)	490 (95.9)
	Died (%)	0 (0)	0 (0)	3 (6.4)	3 (7.7)	10 (8.8)	22 (9.3)	35 (5.8)	56 (6.8)	74 (5.9)	55 (5.1)	39 (2.5)	21 (4.1)
HIV positive	Survived (%)	0	1 (50)	2 (100)	13 (86.7)	56 (78.9)	81 (77.1)	171 (83.8)	164 (81.2)	217 (79.2)	218 (88.3)	224 (89.2)	149 (90.3)
	Died (%)	0	1 (50)	0 (0)	2 (13.3)	15 (21.1)	24 (22.9)	33 (16.2)	38 (18.8)	57 (20.8)	29 (11.7)	27 (10.8)	16 (9.7)

CFR significantly decreased both in children HIV negative and HIV positive (Supplementary Figure 17). The analysis included cases after year 2005 (i.e. from when a sufficient number of cases with data on HIV are available) A separate logistic regression models of pneumonia mortality for HIV negative and HIV positive cases, with year of admission as a covariate found that mortality declined in both populations: HIV negative: adjusted Odds Ratio of mortality per year: 0.90 (95%CI: 0.85, 0.95, p=0.000, n=6304; HIV positive: adjusted Odds Ratio of mortality per year: 0.88 (95%CI: 0.82, 0.94, p=0.000, n=1538).

Supplementary Table 2: Multiple Imputation Mixed effects multivariable regression analysis showing odds ratio (95% CI) for risk factors for mortality in children under 2 months of age, 2-11 and 12-59 months old.

Risk factor	Under 2 months AOR (95% CI)	2-11 months old AOR (95% CI)	12-59 months old AOR (95% CI)
Region			
Northern	-	1.00	-
Central	-	1.13 (0.87 – 1.45)	-
Southern	-	1.50 (1.16 – 1.93)	-
Sex			
Male	-	1.00	1.00
Female	-	1.37 (1.29 – 1.47)	1.38 (1.25 - 1.52)
Pneumonia classification[a]			
Pneumonia	N/A	1.00	1.00
Severe pneumonia	1.00	1.97 (1.26 – 3.10)	1.02 (0.68 – 1.55)
Very severe pneumonia	3.32 (2.71 – 4.06)	10.38 (6.62 – 16.12)	5.26 (3.46 – 7.92)
Pneumocystis jiroveci	5.58 (1.49 – 21.12)[c]	17.81 (10.28 – 30.57)	4.95 (2.03 – 12.18)
Days with symptoms			
Less than 21 days	-	1.00	-
More than 21 days	-	1.37 (1.16 – 1.61)	-
Type of referral			
Self referral	1.00	1.00	1.00
From health centre	1.80 (1.50 - 2.16)	1.59 (1.48 – 1.71)	2.16 (1.88 – 2.48)
Measles in last 2 months			
No	-	1.00	-
Yes	-	1.25 (0.96 – 1.61)	-
Age for weight			
Normal weight	1.00	1.00	1.00
Moderately underweight	3.16 (2.48 – 4.01)	2.20 (2.01 – 2.39)	1.82 (1.57 – 2.10)
Severely underweight	3.63 (2.56 – 5.21)	3.35 (3.03 – 3.71)	3.32 (2.83 – 3.86)
Severe Acute Malnutrition			
Absent	-	1.00	1.00
Present	-	3.13 (2.57 – 3.82)	3.90 (3.22 – 4.76)
Temperature			
Afebrile	1.00	-	-
Febrile (>38°C)	1.45 (1.17 – 1.80)	-	-
Season			
Dry (May - October)	1.00	-	1.00
Wet (November - April)	0.73 (0.62 – 0.86)	-	1.14 (1.02, 1.26)
Respiratory category			
normal	-	1.00	-
Fast breathing[b]	-	0.82 (0.71 – 0.93)	-
Year admitted to hospital Per year, 2001 to 2012	0.92 (0.90 – 0.96)	0.91 (0.90 – 0.93)	0.93 (0.91 – 0.95)
Age in months Per month within age group	0.55 (0.46 – 0.64)	0.95 (0.94 – 0.96)	-

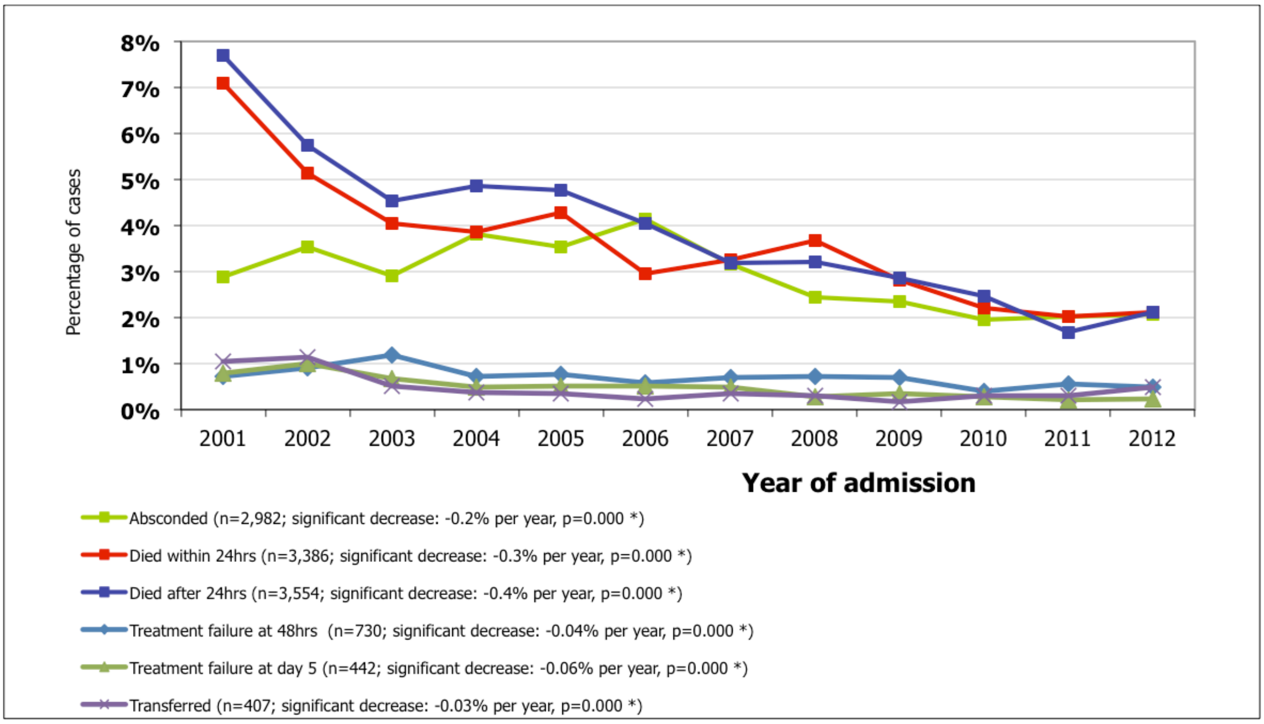
N/A= not applicable
- = not included in final multivariable model
[a] See Panel for definitions
[b] ≥60 breaths/minute if <2 months old, ≥50 breaths/minute 2-11 months old; ≥40 breaths/minute if 12-59 months old
[c] statistically significant at the p<0.05 level with multiple imputation when it was not statistically significant without multiple imputation

Supplementary Figure 18. Trends in variables related to treatment outcomes and mortality

Our primary outcome for this analysis is mortality during hospitalisation in children under 5 admitted for pneumonia. Determining the numerator and denominator for hospital mortality is complicated by the incomplete and sometimes inconsistent filling of the yellow form (Supplementary Figure 1). As the numerator we have used the number of cases for which any of the forms had "Died within 24 hours" or "Died after 24 hours" indicated. As the denominator we have used the number of cases for which we have positive information that the child was either alive or dead at the end of hospitalisation. This comprises cases having a "yes" for any of the following variables from the Discharge and Follow-up and Treatment Results sections: Course of antibiotics to be completed at home, mother informed to return with child once antibiotics completed, child returned for follow-up visit, course of antibiotic completed (this refers to the antibiotics given for home treatment), child fully recovered, treatment completed, left against advice, transferred, and the two death categories (before and after 24 hours) previously mentioned. In instances where none of these variables had been completed, the outcome for total deaths was set to missing. A larger proportion of cases were indicated on the form *as outcome unknown* at time of discharge (Supplementary Figure 18b). In instances of treatment failure, the outcome of mortality was also set to missing. If a child has treatment failure, they will presumably be treated with different antibiotics and any one of the following can happen; they can either improve, they can die, get transferred or abscond. Hence, in cases where the final outcome is treatment failure, we are unsure if the child lived or the child died, with a greater possibility of the child dying than living. For this reason, mortality was set to missing.

The following figures show the trends in each of the variables used to determine treatment outcome and the numerator and denominator of the mortality variable. Supplementary Figure 18a shows significant downward trends in treatment failure at 48hrs and at 5 days as well as in death within 24hrs or after 24hrs, lending support to the decline in CFR shown in Figure 3 of the main paper and supplementary figures 3-14.

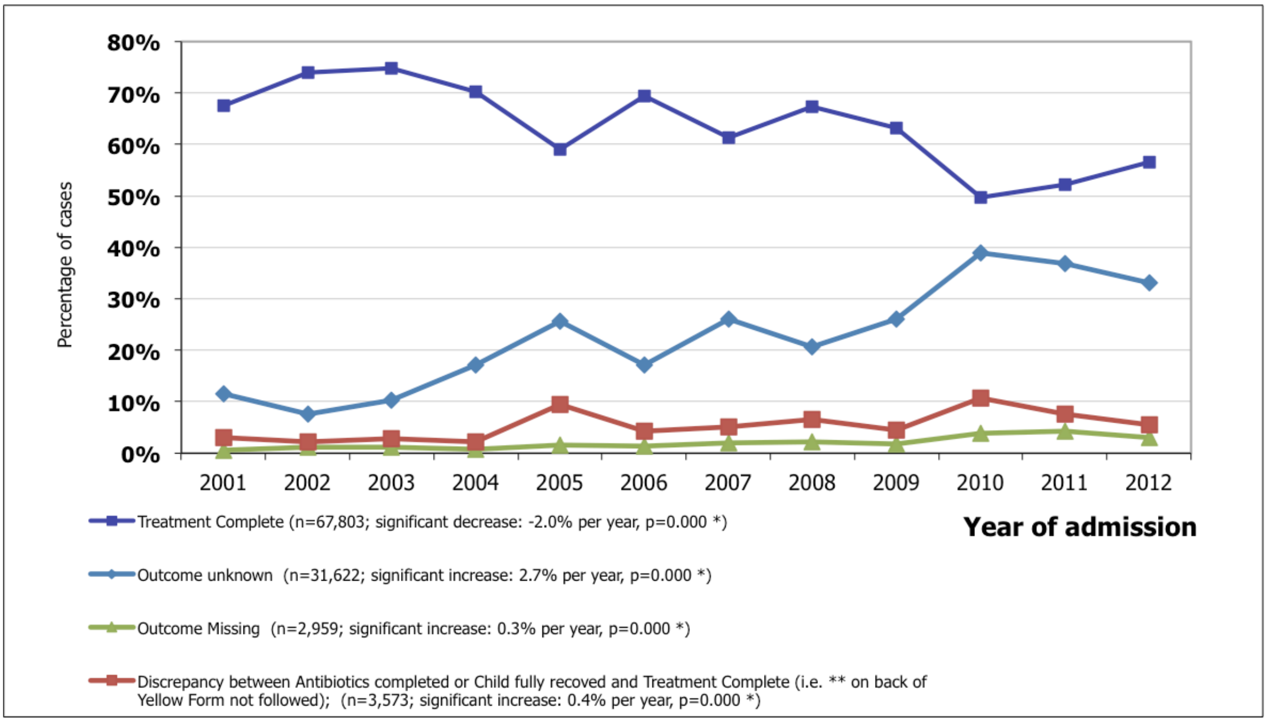
Supplementary Figure 18a. Trends in Absconders, Deaths, Treatment Failure and Transferred Cases



*Trends and associated p-values refer to ordinary least-squares linear regression of the variable on year of admission.

Supplementary Figure 18b, however, shows significant increases in the percentage of cases with unknown outcome at time of discharge (only partially offset by discrepancies in how the form was filled), which mirror the percentage decrease in cases indicated to have completed treatment. This is concerning as it could confound the trend of decreasing CFR. It also matches a general trend for most variables to have more missing data in later years (Supplementary Figure 19).

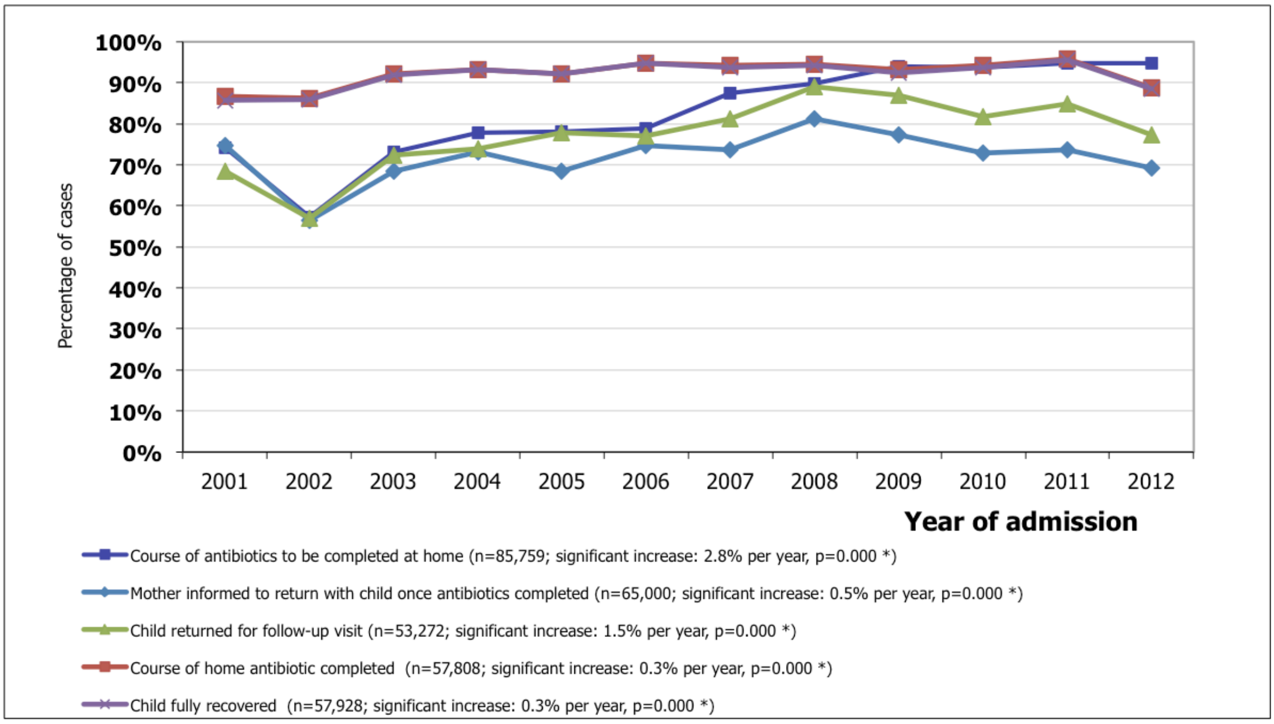
Supplementary Figure 18b. Trends in Treatment Completed and Outcome unknown or missing



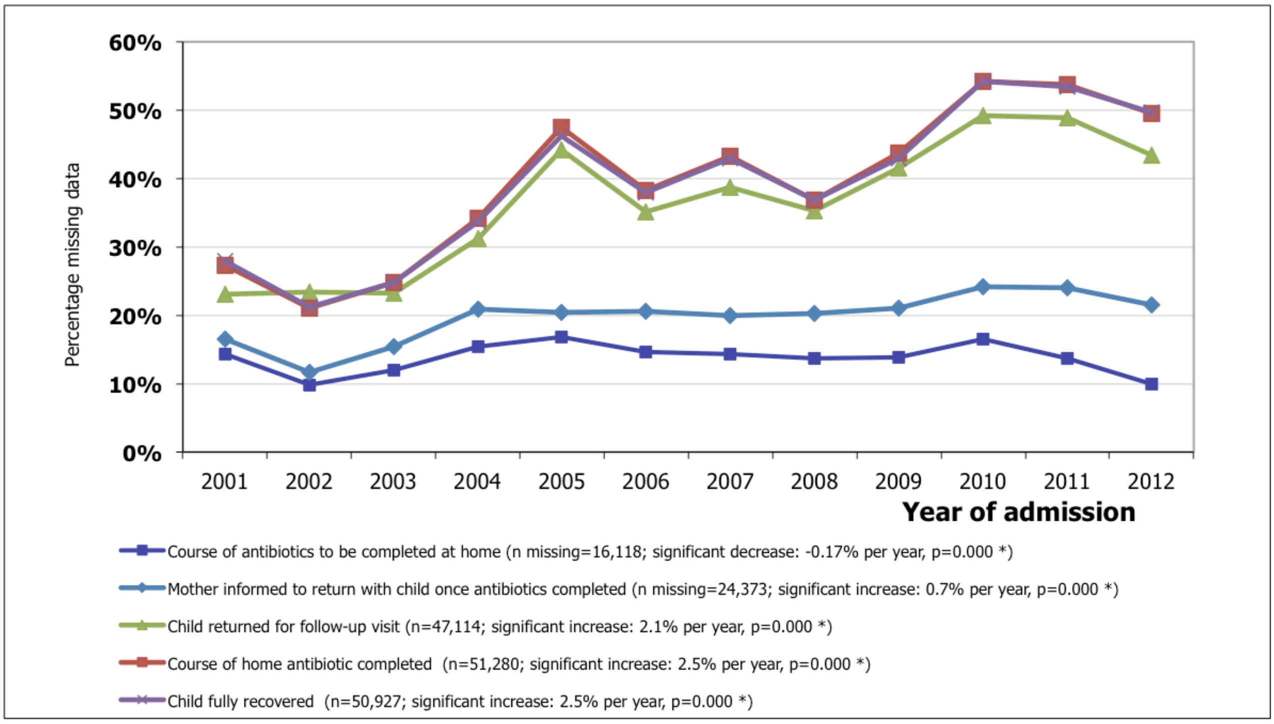
*Trends and associated p-values refer to ordinary least-squares linear regression of the variable on year of admission.

Supplementary Figure 18c shows significant increasing trends in Yes (rather than No responses, see Supplementary Figure 1) to all five of the Follow-up and Discharge variables. Unlike the Treatment outcome variables (Supplementary Figures 18a and 18b) these variables are not mutually exclusive. Therefore we also show trends on the percentage of cases with missing data on each of the five variables in Supplementary Figure 18d. Like many other variables (Supplementary Figure 19), the percentage of cases missing data on these variables are also increasing. This is again concerning as it appears to show a decrease in data quality over time.

Supplementary Figure 18c. Trends in Discharge and Follow-up variables



Supplementary Figure 18d. Trends in Discharge and Follow-up variables missing data



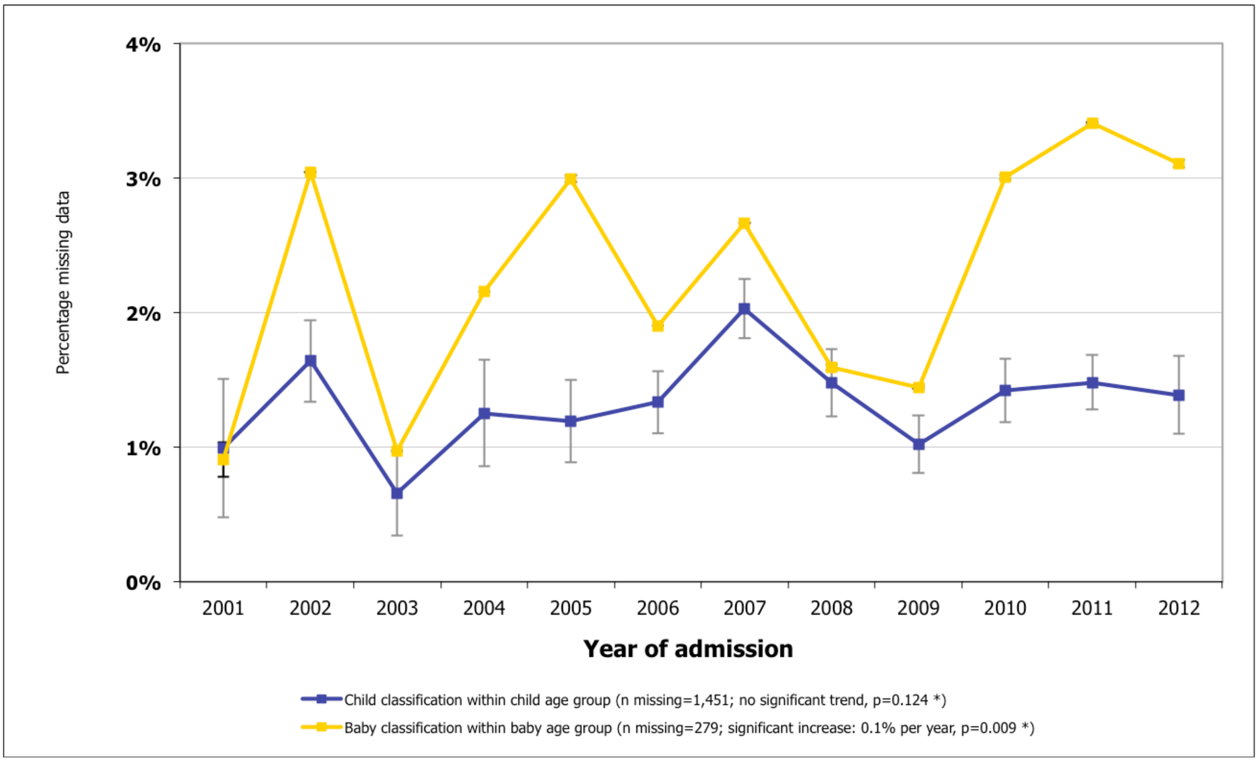
Supplementary Figure 19. Trends in missing data

Supplementary Figure 19a shows no trend in the percentage of cases with missing data on classification of pneumonia in children aged 2-59 months, but does show a slight increase in the percentage of cases missing data on pneumonia classification in babies aged 0-2 months.

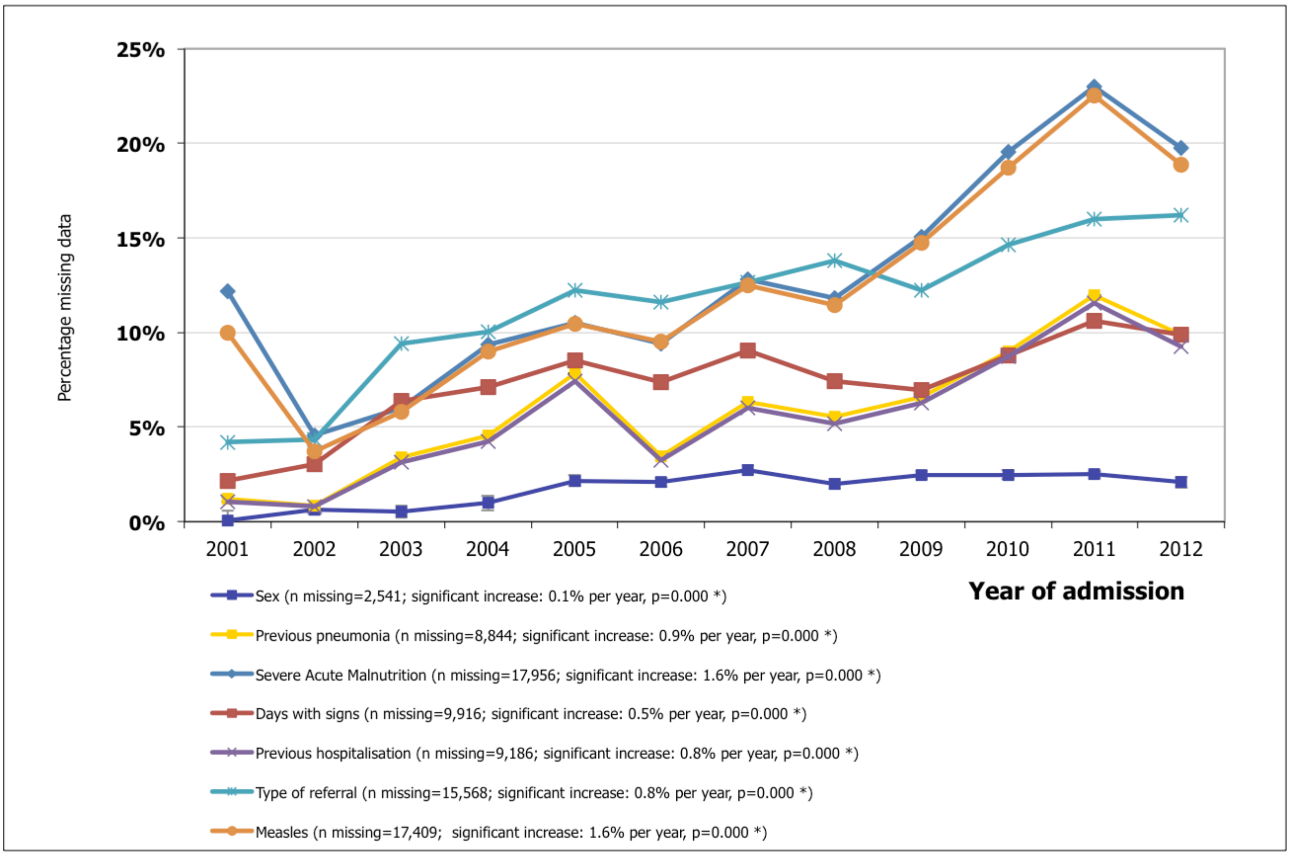
Supplementary Figure 19b shows significant increases, some quite large, in the percentage of missing data for seven of the patient characteristic variables collected on the form that could have been collected independently of clinical examination. Figure 16c shows similar increases for the three variables requiring measurement of the child. If measurements are more likely to be recorded in less severe patients, when the clinician has more time, then these trends could suggest severe cases could be more likely to have been missed in earlier years, meaning our trends in CFR reduction (Figure 2, Supplementary Figures 4-17) could be conservative.

To investigate this we further examined the trends in missing data in the three measurement variables (temperature, respiratory rate, and weight) by splitting them into each of the following four categories of severity of cases: those who died, those with very severe pneumonia, those with severe pneumonia and those with non-severe pneumonia (supplementary figures 19d, 19e and 19f). These figures show significant increasing trends for all four categories of patients, for all three measurement variables, except for weight measurement in non-severe cases. Given the trends in the percentage with missing data do not seem to differ much between dead, very severe, severe and non-severe cases, the increasing trends in missing data over time are unlikely to be a result of changing case mix. Therefore the increase in missing data is more likely to be due to changes in data collection processes.

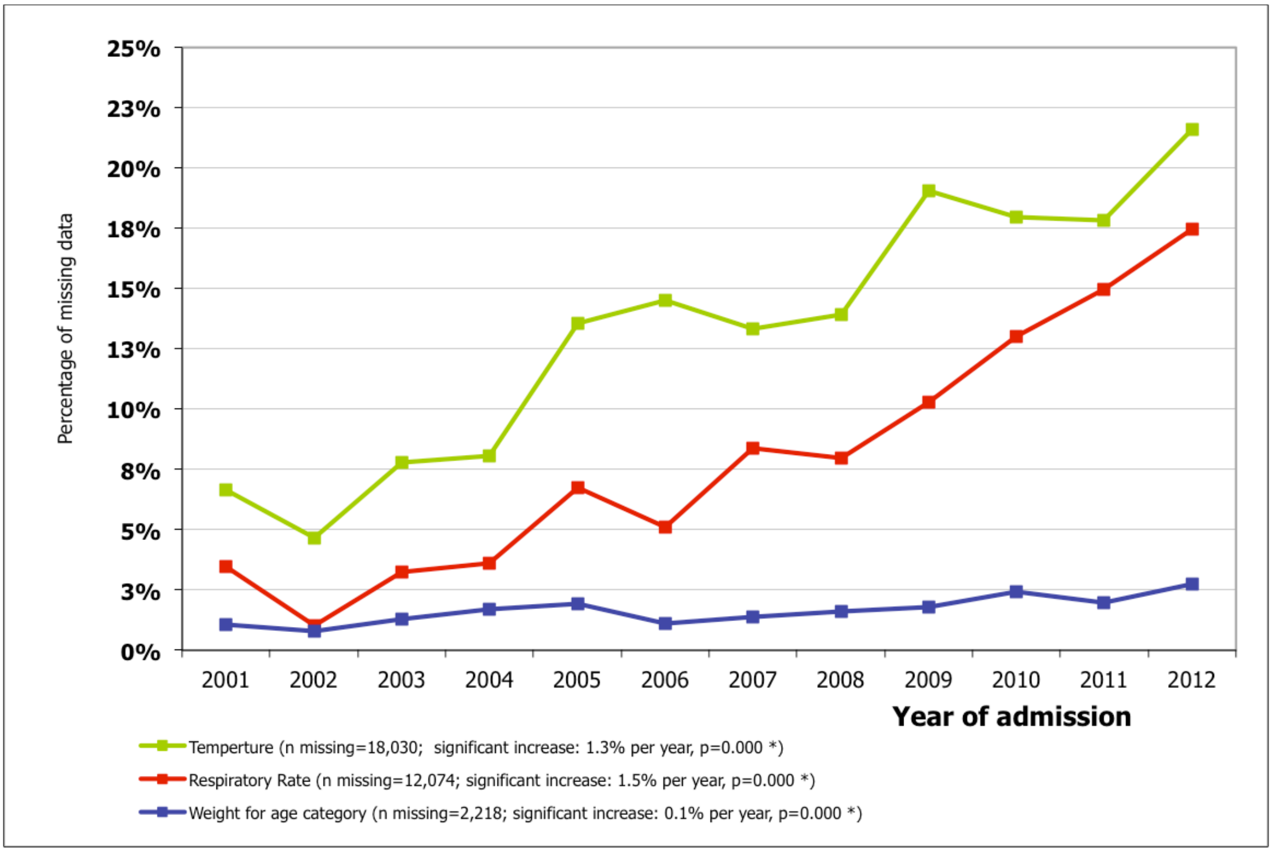
Supplementary Figure 19a. Trends in missing data on the severity classification variables



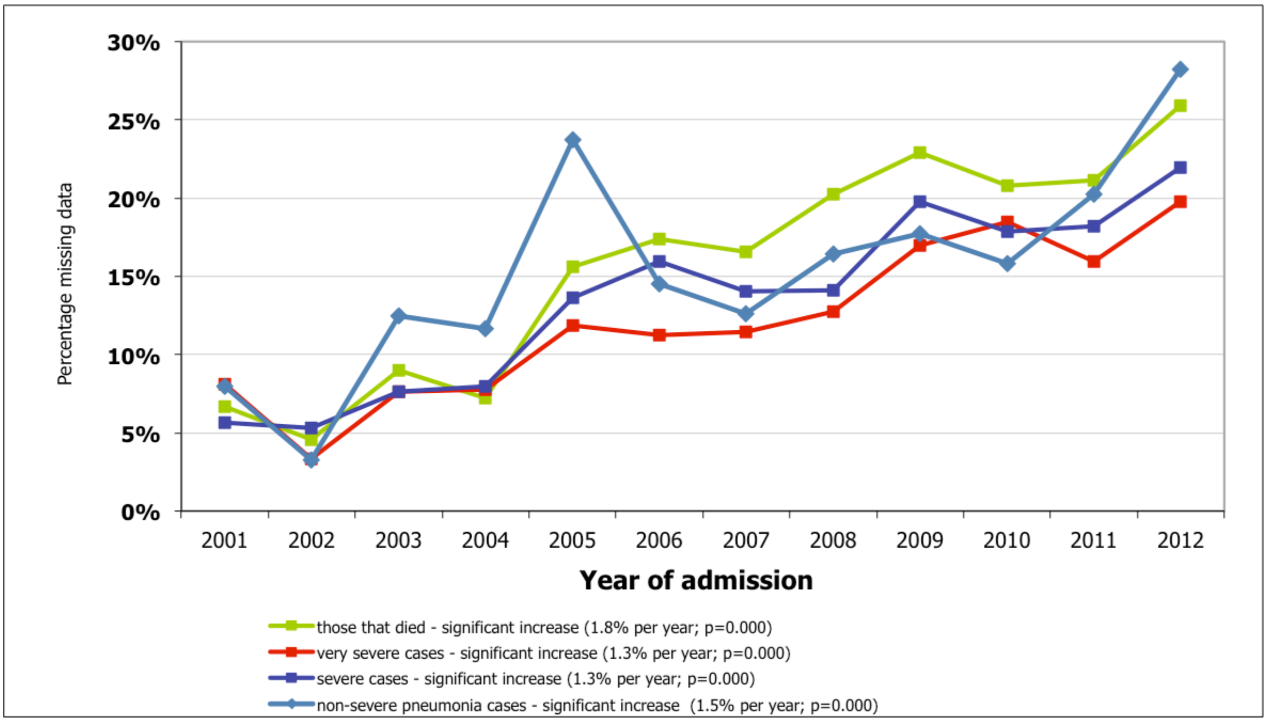
Supplementary Figure 19b. Trends in missing data on variables that could be ascertained independently of clinical examination



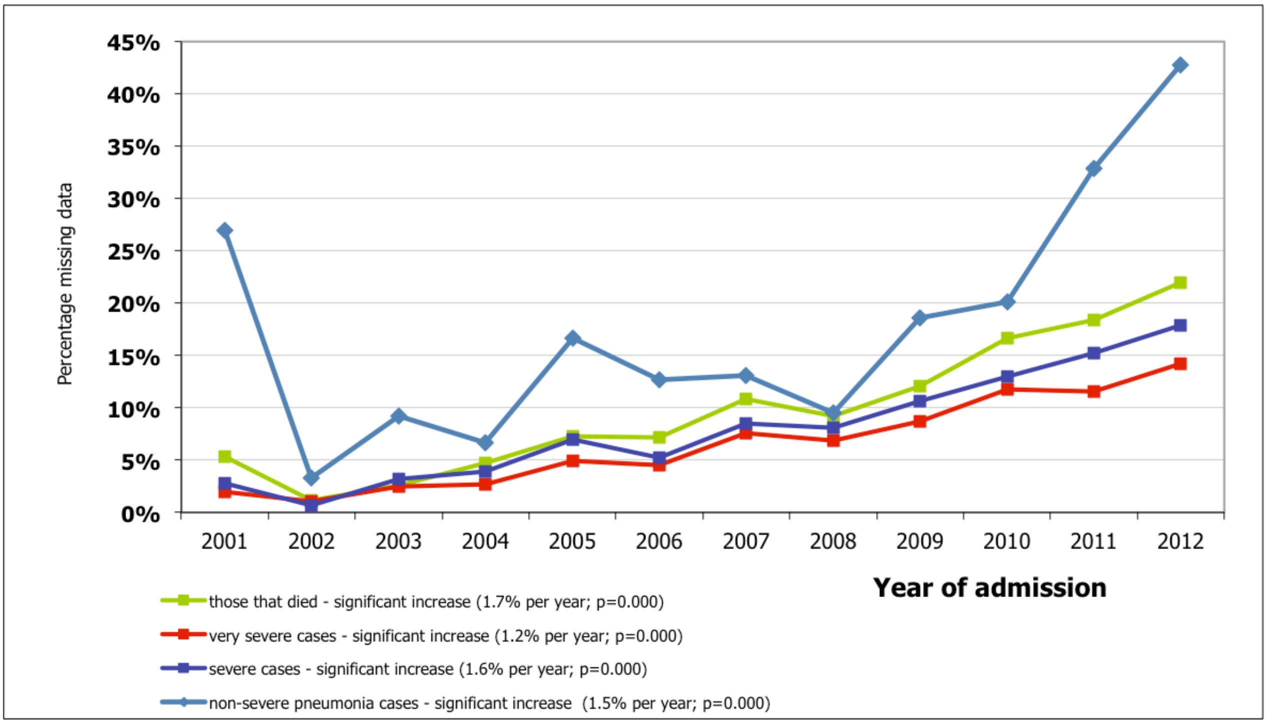
Supplementary Figure 19c. Trends in missing data on variables that require measurement of the child



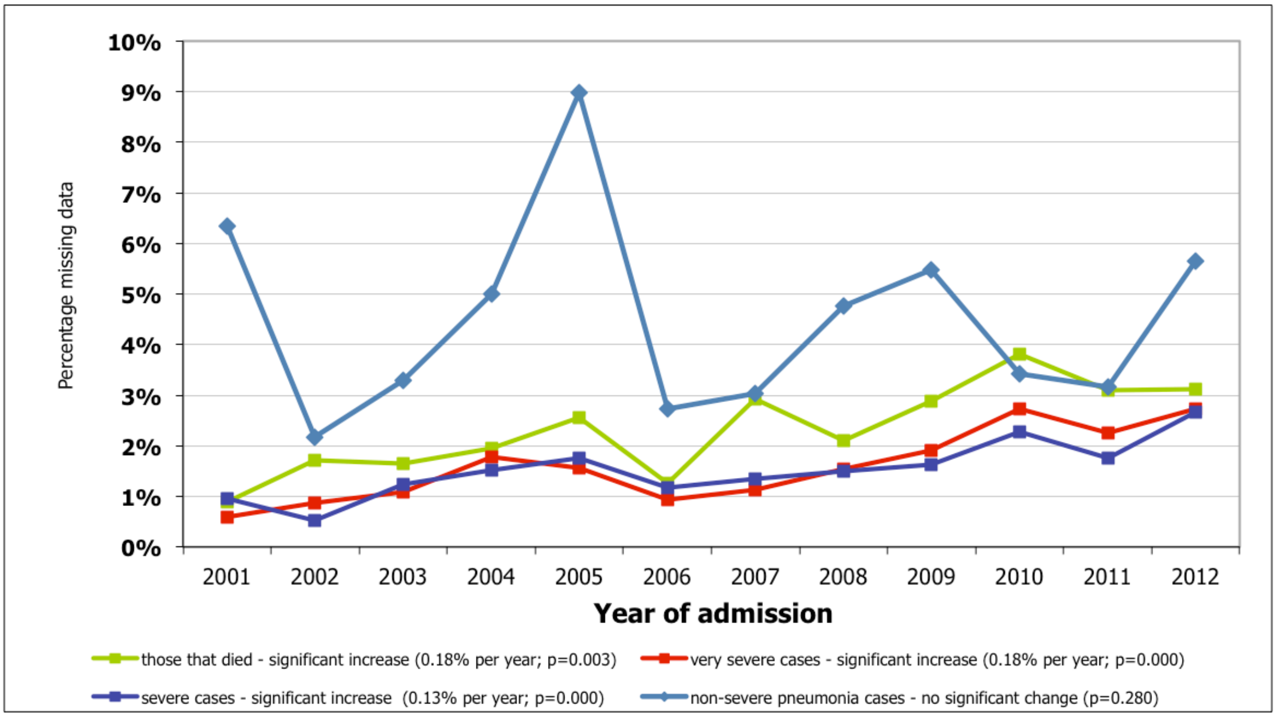
Supplementary Figure 19d. Trends in missing data for temperature measurement, by severity



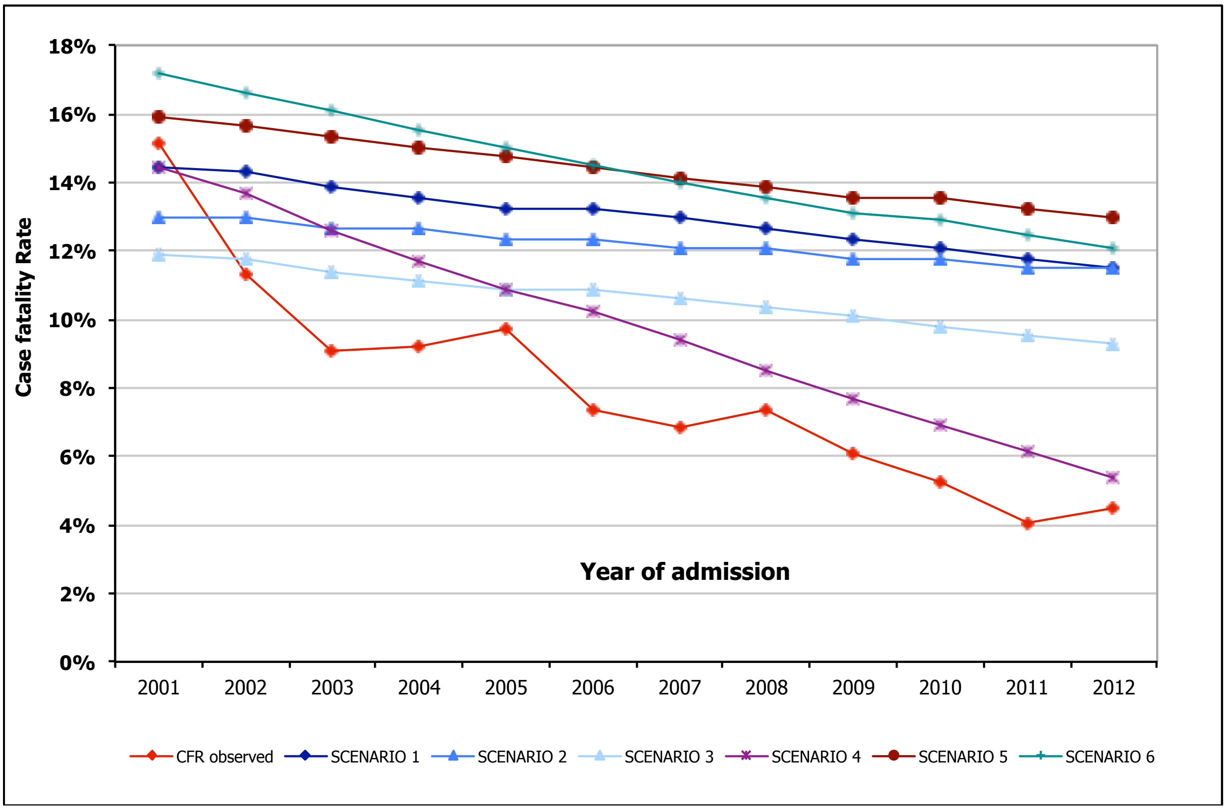
Supplementary Figure 19e. Trends in missing data for respiratory rate measurement, by severity



Supplementary Figure 19f. Trends in missing data for weight measurement, by severity



Supplementary Figure 20. Potential impact of a decreasing trend in HIV prevalence on case fatality rate



Hypothesis used in each scenarios

	Decrease in HIV prevalence from year 2001 to year 2012	CFR in HIV negative	Odds of Mortality in HIV pos compared to HIV neg [8]
Scenario 1	From 15% to 5%	10%	5.9
Scenario 2	From 10% to 5%	10%	5.9
Scenario 3	From 15% to 5%	8%	5.9
Scenario 4	From 15% to 5%	Decreasing from 10% to 4.5% in increments of 0.5% per year	5.9
Scenario 5	From 20% to 10%	10%	5.9
Scenario 6	From 20% to 10%	8%	Decreasing from 7.666 to 4 by increments of 0.333 per year

Supplementary Table 3. Malawi, country indicators in the study period

TYPE OF INDICATOR	YEAR		
BASIC	**2000**	**2010**	**2012**
Mortality rate, under-5 (per 1,000 live births)	164	83	71
Mortality rate, under-1 (per 1,000 live births)	80	53	46
NUTRITION			
Exclusive breastfeeding (% of children under 6 months)	44	71.9	71.4
Low-birthweight babies (% of births)	15.9	12.5	13.5
Underweight, moderate & severe (% of children under 5)	21.5	13.8	12.8
Stunting, moderate & severe (% of children under 5)	54.6	47.8	47.1
Wasting, moderate & severe (% of children under 5)	6.8	4.1	4
GENERAL HEALTH			
Population using an improved drinking water source	62	83	-
Population using an improved sanitation facility	45.5	51	-
Immunization coverage (%), BCG	83	97	99
Immunization coverage (%), DTP3	75	93	96
Immunization coverage (%), MCV	73	93	90
Immunization coverage (%), Hib3	-	93	96
Pneumonia (%), Care seeking for suspected pneumonia	26.7	70.3	70.3
Pneumonia (%), Antibiotic treatment for suspected pneumonia	-	29.5	29.5
Diarrhoea (%), Treatment with oral rehydration salts (ORS)	51.4	69	69
Malaria (%), Antimalarial treatment among febrile children	27	43.4	32.5
Malaria (%), Children sleeping under ITNs	2.9	34.9	56
Vitamin A doses (% of children under 5)	76	40	61
HIV/AIDS			
Children living with HIV (thousands)	-	-	180
Antiretroviral therapy coverage (% of people with advanced HIV)	-	47	69
TUBERCULOSIS			
Tuberculosis treatment success rate (% of registered cases)	73	87	-
Tuberculosis case detection rate (%, all forms)	45	64	68
Incidence of tuberculosis (per 100,000 people)	467	219	163
EDUCATION			
Total adult literacy rate (%)	-	64.8	61.3
Primary completion rate, female (% of relevant age group)	61.8	69.6	74.7
WOMEN			
Antenatal care, at least one visits (% pregnant women)	91.4	94.7	94.7
DEMOGRAPHIC			
Total fertility rate	6.2	5.6	5.5
ECONOMIC			
GNI per capita (current US$)	154	310	320
Health expenditure per capita (current US$)	9.4	28.5	-
Population below international poverty line of US$1.25 per day (%)	65.3	-	61.6
Crop production index (2004-2006 = 100)	98.7	156	-
Food production index (2004-2006 = 100) §	99	157	-
Livestock production index (2004-2006 = 100) §§	92	158	-

§ Food production index: Food production index covers food crops that are considered edible and that contain nutrients. Coffee and tea are excluded because, although edible, they have no nutritive value.

§§ Livestock production index: Livestock production index includes meat and milk from all sources, dairy products such as cheese, and eggs, honey, raw silk, wool, and hides and skins.

Abbreviations: BCG=Bacille Calmette Guerin vaccine; DTP3=third dose of diphtheria, tetanus, pertussis vaccine; Hib3= third dose of haemophilus influenzae type b vaccine; ITNs= Insecticide Treated Nets; MCV= measles containing vaccine

Sources of data: UNICEF Malawi country indicators;[2] The World Bank, World Development Indicators (last update 18 December 2013);[3] Malawi Demographic and Health Survey 2000;[4] Malawi Demographic and Health Survey 2010.[5]

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