Effectiveness of measles vaccination and vitamin A treatment

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Background The current strategy utilized by WHO/United Nations Children's Fund (UNICEF) to reach the Global Immunization Vision and Strategy 2010 measles reduction goal includes increasing coverage of measles vaccine, vitamin A treatment and supplementation in addition to offering two doses of vaccine to all children.

Methods We conducted a systematic review of published randomized controlled trials (RCTs) and quasi-experimental (QE) studies in order to determine effect estimates of measles vaccine and vitamin A treatment for the Lives Saved Tool (LiST). We utilized a standardized abstraction and grading format in order to determine effect estimates for measles mortality employing the standard Child Health Epidemiology Research Group Rules for Evidence Review.

Results We identified three measles vaccine RCTs and two QE studies with data on prevention of measles disease. A meta-analysis of these studies found that vaccination was 85% [95% confidence interval (CI) 83–87] effective in preventing measles disease, which will be used as a proxy for measles mortality in LiST for countries vaccinating before one year of age. The literature also suggests that a conservative 95% effect estimate is reasonable to employ when vaccinating at 1 year or later and 98% for two doses of vaccine based on serology reviews. We included six high-quality RCTs in the meta-analysis of vitamin A treatment of measles which found no significant reduction in measles morality. However, when stratifying by vitamin A treatment dose, at least two doses were found to reduce measles mortality by 62% (95% CI 19–82).

Conclusion Measles vaccine and vitamin A treatment are effective interventions to prevent measles mortality in children.

Keywords Measles, vaccine, vitamin A, treatment

Background

In 2005, the World Health Assembly set a goal of a 90% reduction in measles mortality by 2010 compared with 2000 levels as a part of the Global Immunization Vision and Strategy (GIVS).[1] WHO and UNICEF have instituted a multi-component strategy in 47 priority countries with high measles burden including: reaching and maintaining ≥90% coverage for first dose measles vaccine by 12 months of age, providing appropriate clinical management including vitamin A treatment, enhancing effective measles surveillance,

and monitoring vaccination coverage.[2] In addition, the Strategic Advisory Group of Experts on Immunization recently put forth a global recommendation that all children should receive 2 doses of measles vaccine.[3] Maintaining high vaccination coverage is also central to measles control efforts in countries with relatively low measles burden, and many of these countries will need to increase coverage in order to reach measles elimination goals.

The effectiveness of measles vaccination is based on several host and vaccine factors.[4] The most important factors are age at vaccination and receipt of a second dose.[5] WHO recommends first dose measles vaccination at 9 months of age in many developing countries with a high risk of measles morbidity and mortality during the first year of life.[6] Since 2000, the WHO has also recommended that all children receive a second opportunity for measles vaccination.[2] Most developed countries with low levels of measles transmission vaccinate at 1 year of age or later to minimize the risk of maternal antibody interference, and many have implemented a two-dose schedule. Therefore, the effectiveness of measles vaccine to prevent measles mortality is not uniform worldwide and will vary based on vaccine schedule recommendations and programme implementation strategies. The WHO also recommends vitamin A treatment of measles consisting of two doses of 50 000 IU for infants <6 months of age, 100 000 IU for those 6 months to 1 year of age, and 200 000 IU for individuals >1 year of age.[7] Routine vitamin A supplementation is also thought to decrease measles case fatality in addition to likely reducing mortality from multiple factors, including diarrhoea.[8] The comprehensive Lives Saved Tool (LiST) review of vitamin A supplementation on multiple causes of death determined supplementation decreased measles-specific mortality by 19%.[9]

Multiple reviews of measles vaccine and vitamin A treatment effectiveness have been published.[10–13] However, most measles vaccine reviews have employed serologic data to determine effect estimates for measles-specific mortality. The most recent Cochrane review for vitamin A treatment of children with measles erroneously includes a supplementation trial; therefore, we have revised the analysis excluding this trial.[13,14] Here, we present our systematic review of measles vaccine and vitamin A treatment in order to determine effect estimates and corresponding uncertainty for the LiST.

Methods

We systematically reviewed all published literature from 1960–2008 to identify studies of measles vaccine and vitamin A treatment. As per the Child Health Epidemiology Research Group (CHERG) systematic review guidelines, PubMed, Cochrane Libraries, and all WHO Regional Databases were searched in all languages.[15] The search terms for measles vaccine studies included combinations of 'measles vaccine', 'trial', 'effect*', 'effica*', 'mortality', and 'non-specific'. The vitamin A treatment search terms included: 'vitamin A', 'trial', 'effect*', 'effica*', 'mortality' and 'measles'. Studies abstracted for analysis included randomized controlled trials (RCT) and quasi-experimental (QE) studies due to a priori knowledge of these high-quality studies. Observational studies were included in the all-cause mortality analysis for measles vaccine due to minimal data from RCTs or QE studies. Three studies reported data for two distinct study cohorts using different methods; therefore we chose to analyse the cohorts separately and when referencing these studies denote cohort 'a' and 'b'.[16–18] If two or more studies presented data for the same population during the same time period, the most applicable study based on methods and analysis was included in the meta-analyses. Studies using high-titre measles vaccine were excluded as this vaccine was associated with increased mortality in girls.[19]

All studies which met final inclusion and exclusion criteria were double data abstracted into a standardized form for each outcome of interest.[15] We abstracted key variables with regard to the study identifiers and context, study design and limitations, intervention specifics, and outcome effects. Each study was assessed and graded according to the CHERG adaptation of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) technique.[20] Randomized or cluster randomized trials received an initial score of 'high'. The grade was decreased one grade for each study design limitation. In addition, studies reporting an intent-to-treat analysis or with statistically significant strong levels of association (>80% reduction) received 1–2 grade increases. Any study with a final grade of 'very low' was excluded.

For any outcome with more than one study, we conducted a meta-analysis and reported the Mantel–Haenszel pooled relative risk (RR) and corresponding 95% confidence interval (CI). When there was heterogeneity, the DerSimonian–Laird pooled RR and corresponding 95% CI were reported. If zero events occurred in a treatment group, 0.5 was added to both the treated and untreated event total in order to compute a 95% CI and corresponding P-value. In the meta-analysis of studies with data on the effect of measles vaccine on measles mortality, there were no deaths among the vaccinated; therefore, we chose not to compute an effect estimate with confidence intervals since our method to account for zero events would significantly lower the effect estimate. Results are expressed in terms of relative benefit $(1-RR)$, which is more commonly defined as efficacy or effectiveness. All analyses were conducted using STATA 10 SE statistical software.

We summarized the evidence by intervention and outcome including a qualitative assessment of the

study quality and quantitative measures according to standard guidelines[15] for each outcome. The CHERG Rules for Evidence Review[20] were applied to the collective measles vaccine and vitamin A treatment data to generate estimates for the effect on measles mortality.

Results

We identified 3179 titles from searches in all databases for measles vaccine. After screening, we included three studies with measles-specific mortality data,[16a,16b,21] 23 studies of all-cause mortality,[16b,17,22–41] and nine studies which reported measles disease as an outcome[16a,16b,18,21,42–45] in the final database (Supplementary Table 1). In Table 1, we report the quality assessment of measles vaccine studies by outcome, as well as results from corresponding meta-analyses. In the two RCTs and one QE study with measles specific mortality, no measles deaths occurred in the vaccinated.[16a,16b,21] Next, we included studies that attempted to control for confounding in our meta-analysis for the effect of measles vaccine on all-cause mortality. Thirteen observational studies[25–27,31–33,37,39–41] and one RCT[16b] met these requirements and the results indicate that measles vaccine was associated with a reduction in all-cause mortality of 43% (29–54). Four studies in the original database were excluded from the meta-analysis of vaccination effect on measles disease: an RCT which noted differential misclassification of measles disease by

vaccination status, an RCT that administered immunoglobulin to children in contact with measles, a QE study where a proportion of measles vaccine administered was not potent due to improper storage, and a QE study which did not publish the number of trial participants or confidence interval.[16b,43,44,18b] The five remaining studies, three RCTs and two QE studies, found that a single dose of measles vaccine reduced measles disease by 85% (95% CI 83–87) (Figure 1).[16a,21,42,18a,45]

A total of 270 titles were identified for evaluation of vitamin A treatment. We included seven studies, six RCTs and one QE, in the final database for vitamin A treatment of measles[46–52] (Supplementary Table 2). The Ellison study was excluded from meta-analyses
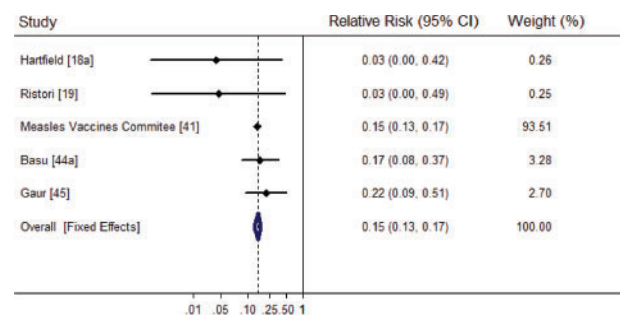

Figure 1 Forest plot for the effect of one dose measles vaccine on measles disease (vaccinated compared with unvaccinated). Heterogeneity $\chi^2 = 3.59$ (df = 4); $P = 0.464$. I^2 (variation in RR attributable to heterogeneity) = 0.0%. Test of RR = 1: $z = 26.34$; $P < 0.01$

Table 1 Quality of evidence assessment for measles vaccine

No. of studies (ref.)	Design	Limitations	Consistency	Generalizability to population of interest	Generalizability to intervention of interest	Intervention	Control	Relative benefit[a] (95% CI)
				Quality assessment			**Summary of findings**	
				Directness		No of events		
Measles Mortality: high outcome-specific quality								
3 (16a, 16b, 21)	2 RCT 1 QE	None	NA	No studies in Asia (−0.5)	Generalizable	0	14	100% (NC)
All-cause Mortality: low outcome-specific quality								
14 (16b, 25–27, 31–33, 35–41)	1 RCT 8 PC 2 RC 3 CC	None	Heterogeneity (−0.5)	Generalizable	Generalizable	297	164	43% (29–54)[b]
Measles Disease: high outcome-specific quality								
5 (16a, 18a, 21, 42, 45)	3 RCT 2 QE	None	No Heterogeneity	Generalizable	Generalizable	203	2238	85% (83–87)[c]

NC, not calculated.
[a]Relative benefit is 1 − RR.
[b]Calculated with DerSimonian–Laird method.
[c]Calculated with Mantel–Haenszel method.

Table 2 Quality of evidence assessment for vitamin A treatment for measles

No. of studies (ref.)	Quality assessment			Directness		Summary of findings		
	Design	Limitations	Consistency	Generalizability to population of interest	Generalizability to intervention of interest	No of events		Relative benefit[a] (95% CI)
						Intervention	Control	
Measles Mortality: moderate outcome specific quality								
5 (46–51)	RCT	None	No heterogeneity	Only African studies (−0.5)	Different doses of vitamin A (−0.5)	19	33	37% (−8 to 63)[b]
Measles mortality (At least two doses of 200 000 IU for children and 100 000 IU for infants): moderate outcome specific quality								
3 (46–48)	RCT	<50 events (−0.5)[c]	No heterogeneity	Only African studies (−0.5)	Generalizable	8	23	62% (19 to 82)[b]

NC, not calculated.
[a]Relative benefit is 1 − RR.
[b]Calculated with Mantel–Haenszel method
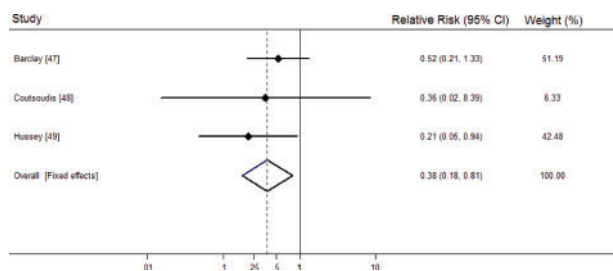[c]Deduction to account for Rule 0 of CHERG Rules for Evidence Review.

Figure 2 Forest plot for the effect of vitamin A treatment on measles mortality for at least two doses of 200 000 IU for children and 100 000 IU for infants (treated vs untreated). Heterogeneity $\chi^2 = 1.05$ (df = 2); $P = 0.592$. I^2 (variation in RR attributable to heterogeneity) = 0.0%. Test of RR = 1: $z = 2.50$; $P = 0.01$

due to lack of randomization and the use of a smaller dose of vitamin A (~3000 IU) compared with the RCTs.[52] A meta-analysis of the six high-quality RCTs found no significant reduction in measles mortality [RR 0.63; 95% CI (0.37–1.08)] (Table 2).[46–51] However, when stratifying the analysis by vitamin A treatment dose, at least two doses of 200 000 IU for children >1 year and 100 000 IU for infants, treatment was found to reduce measles mortality (RR 0.38; 95% CI 0.18–0.81) (Figure 2).[46–48]

Discussion

The WHO estimated that 750 000 measles deaths occurred worldwide in 2000 and decreased to 197 000 in 2007.[53] This substantial reduction is largely due to intense efforts from WHO/UNICEF and other programmes to provide vitamin A supplementation and treatment as well as increase coverage of measles vaccine including offering a second opportunity for vaccination in countries with a high measles burden.

Live attenuated measles vaccine was first introduced in the United States and many developed countries during the 1960s; licensure was based on prevention of measles disease and immunologic correlates of immunity as the primary outcomes.[54–56] Our systematic review identified three RCTs identifying measles-specific mortality as an endpoint. Only 14 measles deaths occurred in the three trials combined (all in the unvaccinated group) and following the CHERG Rules for Evidence Review, we were not able to determine a direct effect estimate.[57] Observational studies, in addition to RCTs, were included in the all-cause mortality analysis to address the hypothesis that measles vaccine has an effect on non-measles mortality.[58] Our meta-analysis found that measles vaccine reduced all cause mortality by 43% (29–54), but the quality of evidence is graded low per CHERG rules due to a majority of data arising from observational studies, which are prone to survival bias and possibly other forms of unrecognized bias. Due to inconclusive evidence for a non-specific effect of measles vaccine on all cause mortality, this assessment will not be included in this edition of LiST. We included three RCTs and two QE studies in the meta-analysis of vaccination effect on measles disease. These studies found that measles vaccine reduced measles disease by 85% (95% CI 83–87) and per Rule 7, this effect size will be used in the LiST tool as a proxy for prevention of measles mortality. Numerous methodologically sound observational studies have also been published with data on the effectiveness of measles vaccine; however, per LiST rules these studies are graded as 'low' and are

considered weaker sources of evidence in comparison to RCTs. Furthermore, a pooled estimate of well-conducted observational studies would likely underestimate the true efficacy of measles vaccine. A substantial proportion of published observational studies were conducted during measles outbreaks which can occur as a result of decreased vaccine efficacy attributable to improper vaccine storage or vaccination of children before recommended age.[5]

Our effect estimate is consistent with the Cutts serology review which estimated seroconversion rates of 85% when vaccine is administered prior to one year and the Singh review which estimated effectiveness of 85–90% based on feasibility studies conducted in India.[10,11] Our effect findings and corresponding uncertainty are applicable to real world vaccine programmes in developing countries as children are vaccinated at a wide range of ages. The studies included in our analysis vaccinated children between 6 months and 5 years. However, this estimate is likely conservative for the effect of vaccination on measles mortality since several studies have documented that previously vaccinated children who develop measles have reduced rates of complications compared with unvaccinated children.[59–61] None of the trials in our meta-analysis specifically address current vaccination programmes in developed countries, where the recommended age of vaccination is usually at $\geqslant 12$ months of age. Measles vaccine is more effective when administered to older children as maternal antibodies that can interfere with development of immunity are usually absent.[62] The WHO SAGE recently recommended that countries with low levels of measles transmission increase the age at administration of the first dose of vaccine from 9 to 12 months in addition to providing a routine second dose during the second year of life.[3] Approximately, 95% of individuals seroconvert when measles vaccine is administered at one year of age or older.[63,64] Therefore, if the LiST tool is used to estimate measles mortality effect in countries vaccinating at one year or greater, the user may want to increase the effect estimate for measles vaccine. In addition, we chose not to include herd immunity in the default LiST estimates for single dose vaccine. The reproductive number (R_0) for measles is 15–20 and >95% of a population is needed to be immune in order to stop endemic transmission.[65] Furthermore, these immune individuals will have to be equally dispersed in the population, an assumption we are not willing to make especially since most developing countries have not reached >90% coverage. However, LiST users have the capacity to adjust the effectiveness of measles vaccination by coverage level, and we support users adjusting country specific effect estimates to 100% if strong surveillance data indicate no measles transmission.

The effect of a second dose of measles vaccine on measles disease or mortality compared with no vaccination has not been evaluated on individual children in prospective randomized studies as this type of trial would be unethical. Therefore, the best estimate of the effect of a two-dose measles vaccine schedule on measles mortality must be extrapolated from serology data, studies looking at effectiveness of two dose vs one-dose measles vaccination, and observational studies. Caution should be taken when using serology data to estimate the impact on mortality. A recent WHO review of serology studies determined that a median 97% [inter-quartile range (IQR) 87–100%] of children that failed to seroconvert to first dose measles vaccine developed immunity after a second dose.[64] If 85% efficacy is assumed for single dose measles vaccine, these serology results would correlate to an efficacy of 99.6% for two dose measles vaccine with a range of 98.1–100% based on the IQR of the review. In addition, the effectiveness of two doses of measles vaccine will vary by setting based on the age of vaccination. Epidemiologic studies comparing the effectiveness of early two dose vaccination vs single dose have found varying results in developing country settings; a study in Niger found two doses (first dose at 6–8 months and second at 9 months) was 23% less effective than single dose whereas studies in India (first dose at 9–12 months and second at 15–18 months) and Guinea Bissau (first dose at 6–8 months and second at 9–12 months) determined two doses of vaccine were respectively 83 and 90% more effective than one dose of measles vaccine.[66–69] In order to produce a conservative estimate of the efficacy of two dose measles vaccine per LiST rules, we felt an input of 98% based on the lower quartile of the WHO two dose measles vaccine serology review was reasonable.

Vitamin A deficiency is a recognized risk factor for severe measles and since 1987 the WHO and UNICEF have recommended vitamin A treatment of children with measles.[70] We performed a meta-analysis of six vitamin A treatment RCTs with measles-specific mortality data and found no significant reduction in measles morality [RR 0.63; 95% CI (0.37–1.08)]. However, when stratifying the analysis by vitamin A treatment dose, at least two doses of 200 000 IU for children $\geqslant 1$ year of age and 100 000 IU for infants was found to reduce measles mortality by 62% [RR 0.38; 95% CI (0.18–0.81)]. These results support the current recommendation that two doses of vitamin A be offered to children with measles.[7] An exception to Rule 0 (at least 50 deaths needed) was deemed appropriate with support of CHERG due to the high quality evidence from three RCTs. As a result, a 62% effect estimate with corresponding uncertainty will be used in the LiST tool.

Intervention	Outcome Measures		Application of Rules
Measles Vaccine ***High quality evidence of morbidity reduction: Highly Plausible Effect**	**Measles Mortality** 3 Studies; 14 events Relative Benefit of 91% (95% CI: 50 to 98)	→	Under 50 Events
	All Cause Mortality 3 Studies; 461 events Relative Benefit of 43% (95% CI: 29 to 54)	→	Low Quality
	Measles Disease 6 Studies; 2441 events Relative Benefit of 85% (95% CI: 83 to 87)	→	Rule 7: APPLY
Vitamin A Treatment ***High quality evidence of measles mortality reduction: Highly Plausible Effect**	**Measles Mortality –All Studies** 5 Studies; 52 events Relative Benefit of 37% (95% CI: -8 to 63)	→	No Significant Effect
	Measles Mortality-Studies using 2 doses 3 Studies; 31 events Relative Benefit of 62% (95% CI: 19 to 82)	→	Rule 1: APPLY (With exception for Rule 0)

Figure 3   Application of standard rules to measles interventions for LiST

The results of our review, which are the default effectiveness values included in LiST, are summarized in Figure 3. Our results support the current strategy of WHO/UNICEF to reduce measles mortality in priority countries, which includes increasing coverage of measles vaccine and vitamin A in addition to offering a second opportunity for vaccination to all children. The GIVS 2010 goals for measles seem to be within reach and hopefully with offering two dose measles vaccine in the South-East Asian region a 90% reduction in measles mortality will be accomplished.

Supplementary data

Supplementary data are available at *IJE* online.

Funding

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