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Beneficial Non-Specific Effects of Measles Vaccine: Fact or Fiction?

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Abstract

Background: A recent Systematic Review claimed that randomised controlled trials (RCTs) showed that there are no beneficial non-specific effects (NSEs) of measles vaccine (MV); i.e. effects not explained by prevention of measles infection. The claim contradicts previous meta-analyses. **Methods:** We examined the reasons for these contradictory views. For ethical reasons there are few RCTs of MV in low-income countries (LIC), mainly trials of standard-titre-measles vaccine (STMV) vs high-titre-measles-vaccine (HTMV) in the 1980-90s and trials of two-dose vs one-dose of STMV in the 2000s. We reanalysed the RCTs taking the effect of subsequent vaccinations into consideration. **Results:** The PLOS One review claimed that there are no NSEs since the RCTs of a two-dose strategy gave a meta-estimate of 1.0. The negative effect of HTMV was considered a specific effect due to an excessive vaccine dose. In our reanalysis, one dose of STMV/HTMV versus control vaccine in the age interval 4-9 months, before controls received routine MV, was associated with a mortality ratio of 0.61 (0.37-0.99). After 9 months, STMV compared with HTMV-followed-by-a-non-live vaccine had a MR of 0.72 (0.55-0.95), significantly better for females than males. **Discussion:** The viral dose explanation of HTMV is not valid as it did not explain why the negative effects only applied to females. The review authors did not take into consideration that most RCTs in LIC experience interactions with vaccine campaigns and subsequent routine vaccinations. When these interactions are taken into consideration, the very RCTs selected by the PLOS One review do in fact show beneficial NSEs of MV. **Conclusion:** NSEs are still critical factors to take into consideration in planning of vaccination policy.

Keywords: high-titre measles vaccine; measles infection; non-specific effects of vaccines; randomised control trials; sex-differential vaccine effects; standard-titre measles vaccine

1. Introduction

A recent meta-analysis by Fournais at al. in PLOS One "*found no support for beneficial non-specific effects of **STMV** (standard-titre-measles-vaccine), but linked **HTMV** (high-titre-measles-vaccine) to increased female mortality*" [1]. The negative effect of HTMV was labelled a specific effect of using too large a dose of vaccine virus. The authors include only randomised controlled trials (RCTs) in their review, since RCTs represent the "highest level of evidence" [1].

These conclusions contradict a WHO-commissioned meta-analysis conducted in 2014 [2] and that Nature made the discovery of beneficial non-specific effects (NSEs) of MV a milestone in vaccinology [3]. Since the public perception of MV is critical we examined how the PLOS One paper reached the opposite conclusion.

MV is a WHO-recommended vaccine, so few ethical committees in low-income countries would approve RCTs comparing MV and placebo. RCTs have therefore only been conducted in special

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circumstances. The two main contexts have been RCTs comparing STMV with the new HTMV in the 1980-90s [4-8] and subsequent RCTs comparing an early two-dose versus a one-dose schedule with STMV [9-12]. The RCTs in Fournais et al.'s review stem precisely from these two situations as discussed below.

We examined the origin of the "beneficial non-specific effects" hypothesis, how the PLOS One paper reached conclusions contradicting previous assessments, and whether the RCTs selected by Fournais et al. showed any indication of NSEs.

2. Material and Methods

Analysis of non-specific effects of vaccines. When analysing NSEs, it is important to keep in mind that NSEs of a vaccine are not a response to a specific pathogen, but a modulation of the immune system which may enhance or reduce responses to subsequent unrelated pathogen exposures [13,14]. These modulations have been shown to be mediated via epigenetic reprogramming of innate immune cells [13]. More specifically for MV trained immunity may be induced via functional and metabolic reprogramming of γδ T-cells [15]. The state of "trained innate immunity" induced by one vaccine can be modified by subsequent vaccinations. Hence, when assessing NSEs of a specific vaccine, the evaluation should be limited to the period until a new vaccine is received [14].

This principle is particularly important in low-income countries where there are many other interventions, which may affect children's immune system. In other words, there is no point in claiming that an RCT solely examined the impact of MV versus placebo, if, during the conduct of the trial, both groups received campaigns with OPV (C-OPV), MV, or other routine vaccinations, which may have affected both randomisation arms. Several studies have shown very marked effect modification after a new vaccine was received, also in MV trials [2,6,8,12,14].

Though Fournais et al. examined RCTs of both mortality and morbidity, we have limited the presentation and discussion to data on mortality since all the original studies proposing NSEs focused on mortality. Mortality estimates are strongly affected when another routine or campaign vaccine is given after the initial trial vaccine. We have therefore censored for these vaccines where the information was available.

The non-specific effect hypothesis for MV. Based on previous reviews of MV [2,14,16], we examine the data on the NSEs of MV, including RCTs, community trials, natural experiments and observational studies.

The PLOS One analysis. Having screened 4315 articles, Fournais et al. found few on the NSEs of MV. There were several RCTs conducted in the US or Europe in the 1950s and 1960s to test killed and/or live MVs, which are not mentioned in the review [17,18]. Hence, their analysis is limited to trials from low-income countries, where potential NSEs on mortality would be most apparent due to the higher load of other infections.

The trials of HTMV included in the PLOS One review correspond to the studies previously included in a meta-analysis of HTMV [19]. All RCTs randomised children at 4-6 months of age to HTMV or control vaccine; at 9 months the HTMV-recipients received a non-live control vaccine and controls received STMV.

The RCTs of STMV included three two-dose trials where children were randomly allocated to two doses of MV at 4 and 9 months of age vs no dose at 4 months and one dose of MV at 9 months of age [9-11].

3. Results

(I) Origin of the non-specific effect hypothesis for MV. The idea of NSEs is simple: vaccines may have effects on morbidity or mortality that cannot be explained by the prevention of the vaccine-targeted disease. The suggestion that MV has NSEs was made 30 years ago based on several

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consistent epidemiological patterns which could not be understood unless MV had beneficial NSEs[20] (Box 1).

Box 1: Non-randomised observations supporting beneficial NSEs

Thirty years ago, before RCTs of measles vaccine (MV) had been conducted, it was argued that MV had beneficial NSEs because several observations on the epidemiology of MV could not be understood unless MV had beneficial NSEs[20]. These observations included: First, MV was associated with stronger reductions in mortality (30-86%) than the proportion of deaths attributed to measles infections. Censoring for measles infection/deaths contributed little to the reduction in mortality associated with MV. Second, major reductions in mortality after MV was supported by studies comparing mortality before and after the introduction of MV; this has been strongly supported in subsequent studies (Table 1). Third, early vaccination and shorter follow-up was associated with stronger beneficial effects. Fourth, the effect appeared to be more beneficial for females than males; this has been strongly supported in subsequent studies[2]. Fifth, these effects were not merely due to positive selection bias due to the best children being vaccinated as a similar effect was not found for DTP. Sixth, MV has beneficial effects in situations

Community trials. The concept was initially generated by studies in Guinea-Bissau, showing major declines in all-cause child mortality after the introduction of MV[20] and similar results in large community trials from DR Congo and Bangladesh [21,22]. In the large community trials from DR Congo and Bangladesh, some districts were allocated to MV and some to no MV. These community trials did not have the usual healthy vaccinee bias, common to observational studies, because districts were allocated to MV or no vaccine. The mortality ratio (MR) for MV versus unvaccinated children in the community trials was 0.29 (0.09-0.98) in DR Congo and 0.51 (0.42-0.62) in Bangladesh, for a combined MR of 0.50 (0.42-0.61).

Natural experiments. Natural experiments, where MV was introduced in a campaign and mortality was compared in the years before-and-after the campaign, contributed to idea that MV had beneficial NSEs. In the four community studies from Senegal, DR Congo, India and Guinea-Bissau [21,23-25] and one hospital study from South Africa[26], the MR for MV-year versus no-MV-year was 0.45 (0.38-0.54) (Table 1). There were no other interventions being introduced in the age group of MV recipients.

Key messages

- A PLOS One review asserted that measles vaccine has no non-specific effects (NSEs)
- Randomised controlled trials (RCTs) of measles vaccine (MV) are rare
- However, one dose of MV had a mortality ratio of 0.61 (0.37-0.99) before 9 months.
- After 9 months, STMV had a mortality ratio of 0.72 (0.55-0.95)) vs HTMV-recipients
- Many observations in low-income settings remain incomprehensible without NSEs

Table 1. Community mortality before and after the introduction of measles vaccine.

Study Site, Country	Age Group (Months)	Years Compared	Mortality Rate or Risk (%) (Deaths/Person-Years/N)		Mortality Ratio of After vs Before (95% CI)
			Before Measles Vaccination	After Measles Vaccination	
Community studies					
Kasongo, DR Congo [21]	7-21	1973-73 vs 1975-77	6.1 (21/346)	2.0 (6/392)	0.34 (0.15-0.76)
Bandafassi, Senegal [23]	9-60	1981-86 vs 1987-88	7.4 (345/4638)	3.7 (76/2026)	0.50 (0.39-0.65)

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Bissau, Guinea-Bissau [25]	6-35	1979 vs 1980	12.7 (77/605)	4.7 (29/615)	0.37 (0.24-0.57)
Ballabgarh, India [24]	12-60	1985 vs 1987	6.9 (25/362)	2.9 (12/414)	0.42 (0.21-0.84)
Hospital study (case fatality in hospital)					
South Africa [26]#	7-36	1977 vs 1978	17.1 (101/591)	7.8 (51/654)	0.46 (0.33-0.63)
Combined					0.45 (0.38-0.54)

Notes: # Nine measles cases (three deaths) are excluded from the 1977 statistics. Abbreviations: CI, Confidence Interval.

In another natural experiment, blood samples were collected from all children who received MV during one year in Bandim [27]. Samples were only analysed two years later; during a short time window, no child had seroconverted having apparently received an inert MV. Outside this window, nearly all children seroconverted. Comparing the two groups of children, the MR for children receiving an active MV compared with an inert MV was 0.33 (0.11-0.97).

Observational studies. In 2014, WHO commissioned a review of the NSEs of Bacillus Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP) and MV. The analysis of MV was based on four RCTs showing a relative risk (RR) of mortality of 0.74 (0.51-1.07) and 18 observational studies indicating a RR of 0.51 (0.42-0.63) for MV versus no MV[2]. The WHO-commissioned meta-analysis of NSEs of BCG, DTP and MV emphasised the until-the-next-vaccine-principle by only assessing NSEs until a new vaccine was provided, wherever information was available to censor for the new vaccines[2]. When measles cases/deaths were excluded from the analysis, the estimated RR hardly changed[20], so prevention of measles infection explained little of the overall effect on survival.

The WHO review concluded that "receipt of BCG and MCV (measles-containing vaccine) reduce overall mortality by more than would be expected though their effects on the diseases they prevent"[2].

(II) The PLOS One review. The authors included only RCTs in their review[1]. The observational studies reporting beneficial NSEs[2] were assumed to be due to confounding.

Fournais et al. identified eight papers representing five RCTs of HTMV and seven papers representing five RCTs of STMV investigating mortality as the primary outcome[1]. Notably, Fournais et al. did not mention several RCTs from Nigeria [28,29] and Guinea-Bissau [30-32] included in previous systematic reviews of MV [2,20]. These RCTs had a combined MR of 0.75 (0.47-1.20) (Supplementary Table 1).

HTMV: All RCTs randomised children at 4-6 months of age to HTMV or control vaccine; at 9 months the HTMV-recipients received a non-live control vaccine and controls received STMV. Fournais et al. assessed the effect of HTMV from 4-6 months to 3-5 years of age, reporting that HTMV was associated with a mortality ratio (MR) of 1.22 (1.02-1.46), the negative effect being strongest for females (1.45 (1.06-1.99))[1]. In their interpretation this was likely due to a too high viral dose in the HTMV, i.e., not a negative NSE[1]. Hence, though *they linked high-titre-measles-vaccine to increased female mortality*"[1], this finding did not support the existence of NSEs of vaccines.

STMV: The RCTs of STMV included three two-dose trials where children were randomly allocated to two doses of MV at 4 and 9 months at age vs no dose at 4 months and one dose of MV at 9 months of age [9-11]. The children were followed from inclusion to 3-5 years of age, with no censoring due to other vaccines. Two small trials[33,34] had incomparable designs and have not been further considered here. Though trial designs were similar, the three RCTs of two doses of STMV had very heterologous results, with the MRs for two-dose vs one-dose schedule ranging from 0.70 (0.52-0.94) to 1.38 (0.92-2.06) (p=0.018). Their meta-analysis of the RCTs of STMV gave an estimate of 1.00 (0.84-1.18).

Hence, they "*found no support for beneficial non-specific effects of standard-titre-measles-vaccine*".

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(III) An analysis of the PLOS One selected RCTs taking other vaccines into account. Fournais et al. did not follow the principle of assessing the NSEs of a given vaccine until the next vaccine is given. We have therefore reanalysed the RCTs included in their review following this principle [14].

Due to similar design, it is possible to compare one MV (HTMV or STMV) with a control vaccine/placebo between 4-9 months of age, before MV is provided to the controls [2].

Effects before 9 months of age. HTMV RCTs. In the RCTs, the HTMV groups compared with controls had a MR of 0.77 (0.49-1.21) from 4-9 months [19]. During these trials, the beneficial NSEs was reduced if DTP was given simultaneously with or after HTMV. If the analysis was censored for receipt of DTP, the MR for one dose of HTMV vs control was 0.20 (0.06-0.65)[19]. These estimates were unchanged if measles infections were censored [19].

Two-dose STMV RCTs. The MR for one-dose of MV versus 0-dose in an analysis of all three data sets [12] was 0.88 (0.55-1.33) (Supplementary Table 2). These trials were implemented while there were numerous C-OPVs, which would affect both the one-dose and the 0-dose group, thus potentially neutralising differences between the randomisation groups (see below). Censoring for C-OPVs, the MR for one-dose vs 0-dose was 0.76 (0.44-1.30).

HTMV and STMV combined. Comparing one MV dose with no-MV, there was a beneficial trend for both HTMV and STMV in the 4-9 months age span. In a meta-analysis of both types of measles vaccines, one dose of MV was associated with a MR of 0.82 (0.60-1.13). When censoring follow-up at receipt of unrelated vaccines (DTP or C-OPV) the combined MR became 0.61 (0.37-0.99).

Effects after 9 months of age. HTMV RCTs. From 9 months of age, the HTMV RCTs were also RCTs of STMV being compared with a non-live-control-vaccine-after-HTMV [6,19]. STMV had a MR of 0.72 (0.55-0.95) compared to the non-live vaccine (Table 2). The higher female mortality in the HTMV group was linked to HTMV-recipients receiving a non-live vaccine (DTP, IPV, or meningitis polysaccharide vaccine) at 9 months of age [6,19]. Supporting that this was NSEs, the beneficial effects of STMV were significantly different for females compared to males (p=0.02) (Table 2). Fournais et al. ascribed the negative effect of HTMV to excessive dose of vaccine virus[1].

Table 2. RCTs of HTMV after the second vaccination at 9-10 months and until end of study.

Study	Non-live vaccine after HTMV	Age (months)	Mortality (deaths/person-years)		Mortality ratio
			STMV (controls)	Non-live vaccine after HTMV	
Bissau EZ1 MT[4]	IPV	10-60	17/632.3	23/644.1	0.76 (0.40-1.41)
Bissau EZ2 MT[5]	IPV	10-48	5/134.3	9/134.0	0.55 (0.18-1.64)
Bissau EZ2 HT[5]	IPV	10-48	9/161.8	11/158.5	0.81 (0.33-1.96)
Gambia EZ HT[6]	IPV	10-36	0.134.7	3/137.2	0
Senegal Cohort 1-16[7]	DTP-IPV+YF	10-60	23/844.0	54/1354.8	0.69 (0.42-1.12)
Senegal Cohort 17-24[7]	DTP-IPV+YF	10-60	20/530.1	22/540.4	0.93 (0.51-1.69)
Sudan[8]	Meningitis	10-36	7/606.8	12/641.8	0.63 (0.25-1.59)
All trials					0.72 (0.55-0.95)
Females					0.53 (0.36-0.79)
Males					1.02 (0.68-1.52)

Abbreviations: DTP, Diphtheria-Tetanus-Pertussis. EZ, Edmonston-Zagreb. MT, Median-Titre. HT, High-Titre. IPV, Inactivated Polio Vaccine. HTMV, High Titre Measles Vaccine. STMV, Standard Titre Measles Vaccine. YF, Yellow Fever.

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Two-dose STMV RCTs. The MR after 9 months of age in the three two-dose RCTs of STMV was 0.99 (0.79-1.25). However, if censored for C-OPV-after-enrolment, the MR for two-doses versus one-dose of STMV was 0.56 (0.34-0.90) after 9 months (Supplementary Table 2) [12]. Hence, C-OPVs reduced the beneficial NSEs of the two-dose MV schedule.

4. Discussion

There are good ethical reasons that there are few RCTs of MV against placebo in low-income countries. But there is no reasonable argument for not reviewing all data available and disregarding all data which is not called an RCT. The fact that a study is called a "randomised controlled trial" does not mean that it necessarily holds the "truth". This is particularly so in low-income settings where there is likely to be numerous other interventions during the conduct of a trial. It is worth emphasizing that in such contexts, where RCTs are impossible, it may actually be more valid to search for observations which imply that there are NSEs or that there are none (Box 1).

Fournais et al.'s dismissal of all NSEs for MV is built on limiting their review to a subset of existing RCTs[1], without any attempt to account for the totality of data. Furthermore, they make two erroneous claims:

First, the claim that the increased mortality associated with HTMV is due to a specific effect of an excessive dose of vaccine virus. This is not possible for several reasons: First, from 4-9 months of age, as described above, the HTMV-recipients had lower mortality than the MV-unvaccinated control group [19]. Second, the negative effect from 9 months of age affected only females, which is common for NSEs [14], whereas it is biologically unlikely that females should suffer significantly more than males from a 5-10-fold higher viral dose. Third, HTMV-recipients, who did not receive DTP after HTMV, did not have excess mortality [6]. So, HTMV *per se* did not induce higher mortality, the subsequent non-live vaccine at 9 months did.

Second, the claim that the meta-analysis of the two-dose STMV trials showed no beneficial NSEs because the mortality ratio for the two-dose vs one-dose group was 1.0. As discussed above, it is strange to focus exclusively on RCTs, when it is difficult to get permission to conduct such trials. The Cochrane handbook suggests that non-randomised studies should be included where RCTs are scarce [35]. Fournais et al. did not include all RCTs (Supplementary Table 1). Importantly, the Fournais-paper ignored that NSEs interact with other interventions. As documented by Hernán and colleagues [36], post-randomisation confounding and selection bias emerge in RCTs. Following children for years, beyond the reception of other vaccines will distort the comparison: the RCTs are no longer comparing MV versus control vaccine but cocktails of different vaccines and interactions in both groups.

The severe limitations of the Fournais-paper become clear when analyses adhere to the principles for studying NSEs [14]. In the RCTs that were dismissed as showing no evidence for NSEs by Fournais et al, there was in fact significant beneficial NSEs of MV: one dose of HTMV or STMV compared with no MV had beneficial effects between 4-9 months of age, when unrelated vaccines were controlled in the analysis. Furthermore, when the control group randomised to receiving STMV at 9 months was compared with children receiving a non-live-vaccine-after-HTMV, STMV had beneficial NSEs which were particularly beneficial for females[19].

5. Conclusions

The claims[1] that beneficial NSEs of STMV are not supported in RCTs and that HTMV was associated with increased mortality due to high viral dose are not correct. The Fournais-paper did not include all RCTs (Supplementary Table 1), wrongly assumed that randomisation eliminates confounding or interactions during follow-up [36], and did not respect the principles for analyses of NSEs used in previous reviews [2,14,20].

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The implications of these analytical oversights are not trivial: Fournais et al.'s dismissal of NSEs can be problematic and increase child mortality if it leads to the withdrawal of MV once measles virus has been eradicated.

The scientific and social focus should be on exploring how the beneficial NSEs of MVs can be used to reduce child mortality, and possibly also adult mortality.

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Data Availability Statement and Ethics Approval: The study was based exclusively on published sources and is therefore available for all. No ethical approval was necessary.

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