Vitamin A in Children Hospitalized for Measles in a High-income Country

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Background: Worldwide medical authorities recommend vitamin A supplementation for severe measles requiring hospitalization; however, evidence supporting its use in high-income countries is lacking. A nationwide vitamin A shortage reported in concomitance with a recent measles outbreak in Italy provided an opportunity to test the effectiveness of vitamin A in a high-income setting, approximating an unbiased allocation.

Methods: We conducted a prospective controlled cohort study involving children admitted for measles to a tertiary-care hospital in Southern Italy. The primary outcome was the duration of fever. Secondary outcomes included the length of hospitalization, rate of complications, need for antibiotic treatment and body temperature.

Results: A total of 108 inpatient children (36% female, median age 16.3 months) were enrolled; 36 received 2 doses of oil-based vitamin A according to age, and 72 matched controls received standard care. There were no significant differences between the study groups in the duration of fever (7.03 ± 2.67 vs. 6.82 ± 3.27, $P = 0.72$), length of hospitalization (median, 5.0 vs. 5.0 days, $P = 0.50$), maximum body temperature (median, 39°C in both groups, $P = 0.23$), rate of organ (69.4% vs. 63.9%, $P = 0.72$) and hematologic complications (41.7% vs. 59.7%, $P = 0.12$), or need for antibiotic treatment (66.7% vs. 61.1%, $P = 0.72$). Overall, vitamin A supplementation did not reduce the risk of any complications (relative risk, 1.33; 95% confidence intervals: 0.59–2.96).

Conclusion: Vitamin A does not change the clinical course of measles infection or the rate of complications in children hospitalized in a high-income country.

Study registration number: EU PAS 31805.

Key Words: measles, vitamin A, children, pediatrics

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Measles is a highly communicable, vaccine-preventable viral infection responsible for potentially severe complications and approximately 100,000 deaths annually worldwide.[1,2] Due to reduced immunization coverage, outbreaks have been recently reported in countries where measles had been considered eliminated.[3–6] Further, wild measles virus infection is expected to cause complications in about 30%–40% of patients, and death in 1–2 children, per 1000.[7] A recent study of children hospitalized for measles in a high-income country reported complications for 83%, as well as a mortality rate of approximately 1%.[8]

Standard treatment for measles consists of supportive care and antibiotic therapy of concomitant bacterial infections.[9] Based on its effectiveness in reducing measles-related morbidity and mortality in developing countries,[10] the World Health Organization (WHO), American Academy of Pediatrics, and United States Center for Disease Control and Prevention (CDC) recommend administration of vitamin A in severe cases, including all those requiring hospitalization.[3,11,12] Similarly, the WHO Regional Office for the Eastern Mediterranean Region included vitamin A in a 4-pronged strategy to achieve the goal of eliminating measles.[13]

However, evidence supporting the use of vitamin A in children living in developed areas is very limited and outdated.[14–17] For example, Ellison reported a reduction of respiratory complications and deaths in children who received high doses of vitamins A and D during hospitalization for measles in England; however, those data were collected approximately 90 years ago.[17]

In Italy, more than 7000 cases of measles were reported during the 2017–2018 outbreak; however, a nationwide vitamin A shortage occurred during the same period, and only a minority of children received the treatment during hospitalization.[18,19]

This scenario approximated an unbiased allocation of vitamin A and provided an ideal opportunity to study its effects in a context in which randomized placebo-controlled trials may be unethical, due to the recommendations of medical authorities, and certainly difficult to perform, due to the rarity of infection. Thus, the present study aimed to compare the course of infection and incidence of complications in measles-infected children who received and did not receive vitamin A during hospitalization in a high-income country.

METHODS

Study Design, Population, and Data Collection

This prospective controlled cohort study was conducted between November 1, 2015 and May 31, 2019 at the Pediatric Infectious Diseases Unit (PIDU) of the University Hospital "Federico II" in Naples, the largest metropolitan area in Southern Italy.

Children under 18 years of age admitted to the PIDU for measles were included in the study. Clinical features compatible with measles included a generalized rash lasting more than 3 days and a temperature >38.0°C, with one or more of the following symptoms: cough, coryza, Koplik's spots and conjunctivitis.

A case of infection was defined by the presence of aforementioned suggestive signs and symptoms, together with positive IgM-antibodies by ELISA assay and/or a measles genome isolated by molecular tests on dried blood spots, urine or oral fluids collected within 10 days from symptoms onset. As established by the WHO strategic plan for measles elimination,[20] biologic samples were centralized at a single WHO-accredited laboratory at the Italian National Institute of Health. Diagnosis confirmation

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was performed through sequencing the highly variable region of nucleoprotein gene *N-450*, and molecular genetic characterization by polymerase chain reaction assay.

Asymptomatic children exposed to measles and those seen in an emergency room or managed at home were excluded from the study, due to lack of follow-up and indication for vitamin A supplementation. Children whose caregivers refuse to sign the informed consent were excluded.

Since the registration of the first measles case, a Microsoft Excel standardized database was used to record demographic information, clinical and laboratory data, duration of fever and hospitalization, the occurrence of any complications, treatments and clinical outcome. The present study was conducted according to STrengthening the Reporting of Observational studies in Epidemiology guidelines, further details regarding methodology and standard definitions of organ or hematologic complications are reported in Supplemental Digital Content 1 (Table); http://links.lww.com/INF/E366.

Intervention

All children admitted to the PIDU received supportive care and antibiotics, when needed. During several months of the measles outbreak, the Italian Medicine Agency reported that all products containing vitamin A as single, oral and fixed-dose preparation were temporarily unavailable in the national market.[19] However, a departmental pharmacy retrieved stockpiles (within its expiry date) from territorial pharmacies, and based on the local availability of products containing vitamin A, children admitted between November 2015 and June 2016, and subsequently between March and September 2018 and March and May 2019, received vitamin A in adjunct to standard care.

During those periods, an oil-based preparation of vitamin A was administered orally the first and second day after admission, and always within 5 days from symptom onset to all children admitted for measles. According to guidelines, daily dosage was based on each child's age: 50,000 UI for infants below 6 months, 100,000 UI for infants 6–11 months of age, and 200,000 UI for children 1 year of age or older.[7,14,15]

For each child who received vitamin A, 2 measles-infected children matched for age, gender, presence of underlying chronic conditions and season of hospitalization (winter season from October 1 to March 31, or summer season from April 1 to September 30), and who received standard care in the same department served as controls (1:2 ratio).

A follow-up visit was scheduled approximately 2 weeks after hospital discharge.

Outcome Measures and Sample Size Calculation

The duration of fever in patients who received or did not receive vitamin A, was considered the primary outcome and used to calculate sample size and study power.

Fever is an objective parameter, easily reported by families before admission, simple to measure during hospitalization and closely related to the duration of infection.[21] According to recent national data,[8] the mean duration of fever for measles in children was 6.68 ± 2.69. According to a previous meta-analysis[10] and a study by Kawasaki et al,[16] vitamin A supplementation may reduce the duration of fever by 1.5 days. Considering this effect to be clinically relevant, and assuming an alpha error of 5% with a sampling ratio of 1:2, we initially estimated a study power higher than 80%, with the enrollment of 116 children (39 receiving vitamin A supplementation and 77 receiving standard care). However, since May 2019, the number of measles cases has significantly dropped in Italy, and no other children were hospitalized in the PIDU. We were able to record data of 36 children who received vitamin A, while 72 children were admitted for measles to the PIDU and received only standard care, due to the vitamin A shortage resulting in a study power slightly below 80%. Both in sample size and in the statistical analyses we followed a "superiority" approach with a null hypothesis of equality between the 2 treatment arms and a 2-sided significance level.

The length of hospitalization, the incidence of complications, need for antibiotic therapy, highest body temperature recorded during infection and side effects attributable to vitamin A were considered secondary outcomes.

Statistical Analysis

Quantitative variables were reported as means ± SDs, and variables with skewed distributions were presented as medians and interquartile ranges (IQRs). Continuous variables were compared using a *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were summarized and reported as frequencies and percentages and compared through Fisher's exact test or a χ^2 test, as appropriate. Relative risk (RR) with 95% confidence intervals (95% CI) was used to express the probability that exposure to vitamin A or standard care may reduce the incidence of complications. A Forest plot was used to report the risk of different complications. Two-sided *P* values <0.05 were considered statistically significant. The statistical platform R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

Missing Data Handling

A small number of missing data was ascertained only for the secondary outcome of highest body temperature (n = 10; 9.3%). The primary analysis was thus undertaken under the principle of the complete case analysis, subsequently, results were adjusted according to a sensitivity analysis.

Ethical Statement

The study protocol was approved by the "Ethical Committee Federico II" of the University of Naples, Italy. The study was conducted according to the principles expressed in the Declaration of Helsinki. Patients' caregivers signed specific informed consent, and all patients' data were analyzed and reported anonymously by using a single patient code. The study has been registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

RESULTS

Among the 121 children hospitalized for measles during the observation period, 108 were included in the study (See Figure, Supplemental Digital Content 2; http://links.lww.com/INF/E366). From this group, 36 received 2 doses of vitamin A according to age (36% female, median age 16.5 months), while the other 72 matched children received standard care and served as controls (Table 1).

Most children were of Caucasian ethnicity, 9 children were of Romani origin, and 2 were of African origin, with no significant differences in distribution among the treatment groups (Table 1). Underlying chronic conditions were observed in about one of 5 children and were similarly distributed among the groups (Table 1).

Approximately 95% of the children were not immunized for measles, 6 patients (5.5%) had received a single vaccination dose, and none had completed the immunization schedule. However, because almost half the population was below the age threshold required by law for receiving the first measles immunization dose (48 children were younger than 15 months), 28.7% showed a measles immunization schedule adequate for their age.

TABLE 1. Overall Characteristics, Clinical Features and Immunization Status of the Study Population

Characteristics	Total (n = 108)	Vitamin A Supplementation (n = 36)	Standard Care (n = 72)	*P*
Female, n (%)	39 (36.1)	13 (36.1)	26 (36.1)	1.00
Median age (IQR), months	16.3 (9.8–60.1)	16.5 (9–56.5)	16.3 (10.2–60.9)	0.83
Enrollment during winter season*, n (%)	50 (46.3)	17 (47.2)	33 (45.8)	1.00
Caucasian, n (%)	97 (89.8)	34 (94.4)	63 (87.5)	0.33
Underlying chronic conditions, n (%)	21 (19.4)	7 (19.4)	14 (19.4)	1.00
Measles immunization				
No doses of measles vaccine, n (%)	102 (94.5)	35 (97.3)	67 (93.1)	0.66
One dose of measles vaccine, n (%)	6 (5.5)	1 (2.7)	5 (6.9)	
2 doses of measles vaccine, n (%)	0 (0)	0 (0)	0 (0)	
Measles viral genotype				
Genotype D8	17 (15.7)	12 (33)	5 (6.9)	<0.01
Genotype B3	22 (20.4)	1 (2.7)	21 (29.1)	
Not detected	69 (63.8)	23 (63.8)	46 (63.8)	
Days of fever before admission, median (IQR)	2 (1–4)	2 (1.5–3.5)	3 (1–5)	0.30
Clinical outcome, n (%)				
Discharged without sequelae	106 (98.1)	36 (100)	70 (97.2)	0.55
Discharged with sequelae	2 (1.9)	0 (0.0)	2 (2.8)	
Need of intensive care assistance/death	0 (0.0)	0 (0.0)	0 (0.0)	

IQR indicates interquartile range.

Molecular confirmation of infection was obtained for all patients; however, viral genotype characterization was available only for 39 (36%) children, with B3 genotype detected in 20% of the children, and D8 in 16% (Table 1). Distribution of viral genotypes varied according to the time of enrollment and significantly varied among the study groups. However, the distribution of relevant clinical outcomes was not related to specific measles genotype: the duration of fever in children with B3 was 7.18 ± 3.1 and in D8 6.94 ± 3.15 days ($P = 0.81$), similarly the median length of hospitalization was 5[4,7] and 6 (4.5–11.5) in the 2 groups of patients ($P = 0.28$).

Primary Outcomes

In the overall study population, fevers lasted 6.89 ± 3.07 days, on average. Fever duration was similar between children who received vitamin A and those who received standard care (Fig. 1 and Table 2), with no difference between the 2 groups in the number of febrile days before and after admission (Table 1).

According to subgroup analysis, vitamin A supplementation did not have any impact on primary outcomes for children <24 months, patients with known measles contact, or those affected by chronic underlying conditions (Table 2). No difference in duration of fever was observed between children who received vitamin A supplementation and those who did not, within 48 hours after fever onset (6.44 ± 1.72 vs. 6.70 ± 2.93, $P = 0.73$) or afterward (7.36 ± 3.26 vs. 7.12 ± 3.05, $P = 0.82$). Only 7 children had a weight-for-age <2 SD, the duration of fever was similar in the single child who received vitamin A and in the other 6 receiving standard care (9 vs. 8.6 ± 5.6 days, respectively, $P = 1.00$), although the paucity of data does not allow to draw conclusions.

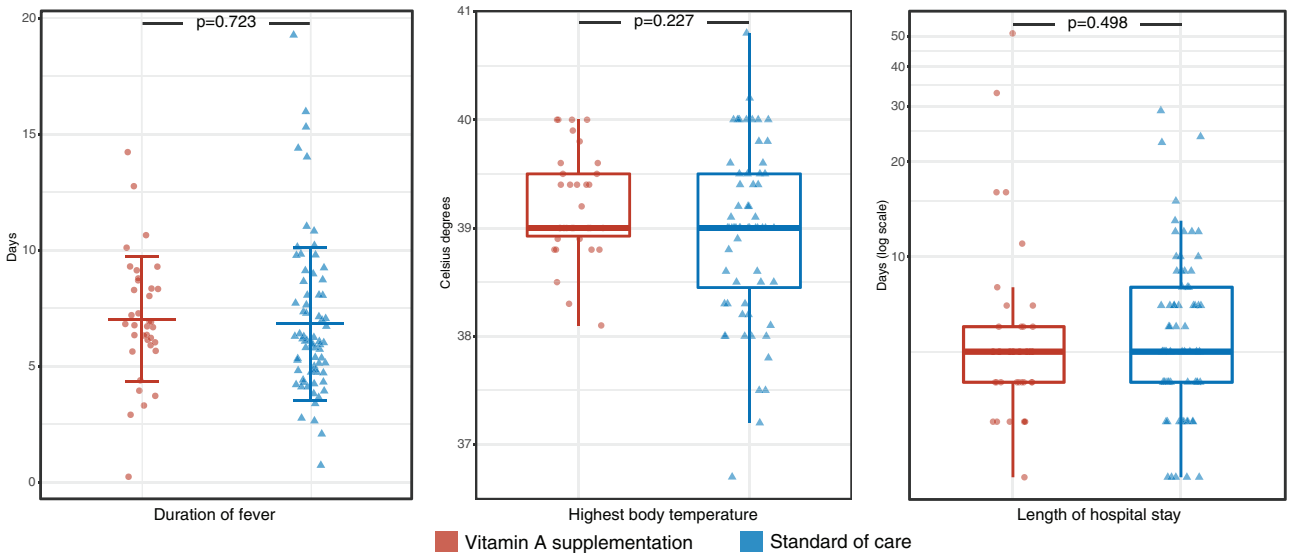

FIGURE 1. Association of vitamin A supplementation and the duration of fever, body temperature, and length of hospitalization in children admitted for measles. A, Mean ± 1 SD of duration of fever in the 2 samples; (B and C) the boxplot of the corresponding variables (body temperature, and length of hospitalization) in the 2 samples. *P* values were obtained using the *t* test in panel A and with the Wilcoxon-Mann: Whitney test on panels B and C. full color online

TABLE 2. Association of Vitamin A Supplementation with Primary and Secondary Outcomes

Outcomes	Total (n = 108)	Vitamin A Supplementation (n = 36)	Standard Care (n = 72)	*P*
Primary outcomes (n = 108)				
Total duration of fever (d), mean (SD)	6.89 (3.07)	7.03 (2.67)	6.82 (3.27)	0.72
Secondary outcomes (n = 108)				
Length of hospitalization (d), median (IQR)	5 (4–7)	5 (4–6)	5 (4–8)	0.50
Any complication, n (%)	88 (81.5)	28 (77.8)	60 (83.3)	0.66
Organ complications, n (%)	71 (65.7)	25 (69.4)	46 (63.9)	0.72
Hematologic complications, n (%)	58 (53.7)	15 (41.7)	43 (59.7)	0.12
Need of antibiotic treatment	68 (63.0)	24 (66.7)	44 (61.1)	0.72
Highest body temperature (°C), median (IQR)	39 (38.8–39.5)	39 (38.9–39.5)	39 (38.3–39.5)	0.23*
Subgroup analysis				
Children below 24 months of age	Total (n = 67)	Vitamin A supplementation (n = 23)	Standard care (n = 44)	*P*
Duration of fever (d), mean (SD)	6.54 (2.88)	7.04 (3.11)	6.27 (2.76)	0.32
Length of hospitalization (d), median (IQR)	5 (3.5–7)	5 (3–7)	5 (3.2–7.8)	0.81
Any complication, n (%)	50 (74.6)	16 (69.5)	34 (77.3)	0.69
Organ complications, n (%)	39 (58.0)	15 (65.2)	24 (54.4)	0.56
Hematologic complications, n (%)	26 (38.8)	5 (21.7)	21 (47.7)	0.07
Need of antibiotic treatment, n (%)	36 (53.7)	14 (60.9)	22 (50.0)	0.56
Highest temperature (°C), median (IQR)	39 (38.5–39.5)	39.1 (38.9–39.5)	39 (38.2–39.6)	0.26
Children with underlying chronic conditions	Total (n = 21)	Vitamin A supplementation (n = 7)	Standard care (n = 14)	*P*
Duration of fever (d), mean (SD)	8.00 (3.98)	8.29 (3.03)	7.86 (4.48)	0.80
Length of hospitalization (d), median (IQR)	7 (5–10)	5 (4–16)	7 (5–9)	0.73
Any complication, n (%)	19 (90.5)	6 (85.7)	13 (92.9)	1.00
Organ complications, n (%)	14 (66.7)	4 (57.1)	10 (71.4)	0.64
Hematologic complications, n (%)	16 (76.2)	5 (71.4)	11 (78.6)	1.00
Need of antibiotic treatment, n (%)	17 (81.0)	6 (85.7)	11 (78.6)	1.00
Highest temperature (°C), median (IQR)	39 (38.8–39.3)	39 (38.8–39.4)	39 (38.1–39.4)	0.93
Children with known measles contact	Total (n = 56)	Vitamin A supplementation (n = 20)	Standard of care (n = 36)	*P*
Duration of fever (d), mean (SD)	6.48 (3.09)	6.30 (2.38)	6.58 (3.45)	0.72
Length of hospitalization (d), median (IQR)	5 (4–7)	4.5 (3.2–5.8)	6 (4–8.8)	0.06
Any complication, n (%)	42 (75.0)	13 (65.0)	29 (80.6)	0.33
Organ complications, n (%)	35 (62.5)	13 (65.0)	22 (61.1)	1.00
Hematologic complications, n (%)	22 (39.3)	5 (25)	17 (47.2)	0.18
Need of antibiotic treatment, n (%)	33 (58.9)	13 (65)	20 (55.6)	0.69
Highest temperature (°C), median (IQR)	39 (38.5–39.5)	39.2 (38.8–39.6)	39 (38.3–39.5)	0.30
Children admitted within 48 h after fever onset	Total (n = 46)	Vitamin A supplementation (n = 18)	Standard of care (n = 28)	*P*
Duration of fever (d), mean (SD)	6.66 (1.82)	6.44 (1.72)	6.70 (2.93)	0.71
Length of hospitalization (d), median (IQR)	5 (4–7)	4.5 (4–6)	5.5 (4–9)	0.07
Any complication, n (%)	40 (87.0)	15 (83.3)	25 (89.3)	0.67
Organ complications, n (%)	37 (80.4)	14 (77.8)	23 (82.1)	0.72
Hematologic complications, n (%)	22 (47.8)	7 (38.9)	15 (53.6)	0.50
Need of antibiotic treatment, n (%)	31 (67.4)	11 (61.1)	20 (71.4)	0.68
Highest temperature (°C), median (IQR)	39 (38.9–39.8)	39 (38.8–39.8)	39 (38.6–39.8)	0.79

*Missing n =10, no difference in results was observed after application of sensitivity analysis.

IQR indicates interquartile range.

Organ complications included: pneumonia, hepatitis, pancreatitis, myocarditis and diarrhea. Hematologic complications included: leukopenia, lymphocytopenia, neutropenia, thrombocytopenia. Definition and frequency of any single complication are reported in Supplemental Digital Content; http://links.lww.com/INF/E366.

Secondary Outcomes

More than 80% of the children developed at least one complication during hospitalization and follow-up. Respiratory illnesses and diarrhea were the most frequently observed complications, affecting 54 (50%) and 19 (17.6%) patients, respectively. The distribution of single complications is reported in Appendix (see Table, Supplemental Digital Content 3; http://links.lww.com/INF/E366).

Despite the high rate of complications, only 2 patients (1.9%) were discharged with permanent sequelae (Table 1). A 5-year boy experienced acute measles-related encephalitis complicated by venous thrombosis that resulted in partial deafness and speech impairment, and an 11-year-old girl had severe otitis complicated by mastoiditis and hearing impairment. No fatal cases were recorded during observation.

Children who received standard care or vitamin A supplementation showed a similar rate of complications (Table 2). A Forest plot depicts the RR of "no complications" after exposure to vitamin A or standard care (Fig. 2) and shows that vitamin A supplementation did not reduce the risk of developing complications.

A trend toward reduction of overall hematologic complications was observed in children who received vitamin A, compared with standard care (41.7% vs. 59.7%, $P = 0.12$). However, the rates of neutropenia, leucopenia and thrombocytopenia did not differ between children who received vitamin A and those who did not (see Table, Supplemental Digital Content 3; http://links.lww.com/INF/E366).

Sixty-eight children (63%) received an antibiotic prescription during hospitalization (see Table, Supplemental Digital Content 4; http://links.lww.com/INF/E366), with 43 (39.8%) receiving oral antibiotics and the others (23.1%) intravenously. Antibiotic treatment lasted a median of 7 days (IQR 2). No significant differences in the need for antibiotics or any other treatment were observed between the study groups (Table 2, and Supplemental Digital Content 4 (Table); http://links.lww.com/INF/E366).

Similarly, the length of hospitalization and body temperature recorded during the infection had a similar distribution between the

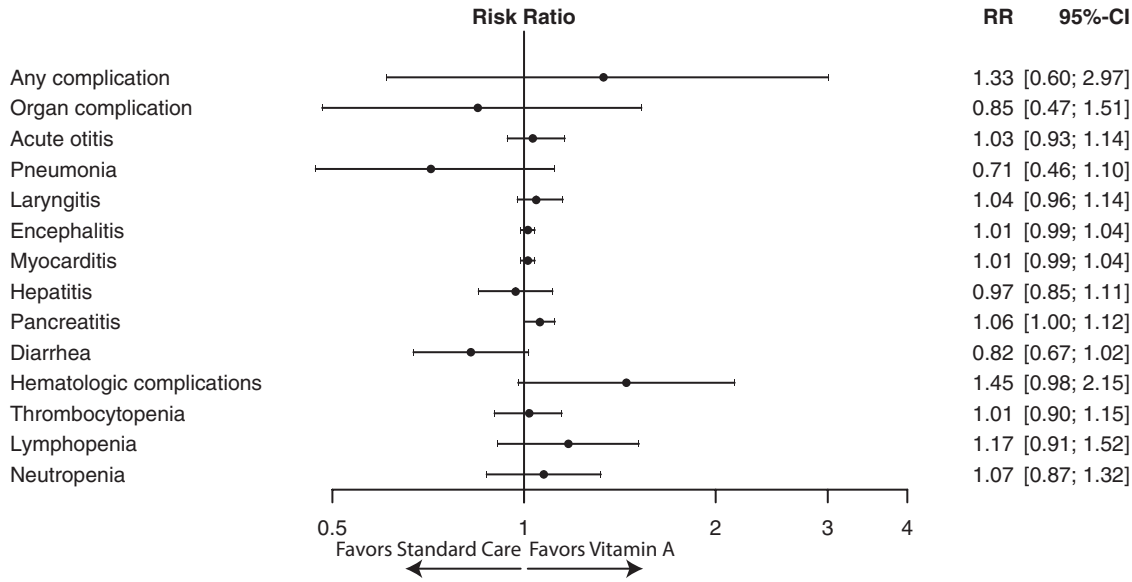

FIGURE 2. Forest plot reporting the ratio of the probabilities of no complications (relative risk with 95% confidence intervals) for children who received or did not receive vitamin A supplementation. CI indicates confidence interval; RR, relative risk.

groups (Table 2). Subgroup analyses performed for children with underlying chronic conditions, weight-for-age <2 SD, known measles contact, or who received care within 48 hours after fever onset, did not demonstrate any benefits of vitamin A over standard care (Table 2).

No adverse events attributable to vitamin A intake were observed during the study period.

DISCUSSION

To our knowledge, this is the first English-language study to report the effects of vitamin A supplementation in children hospitalized with measles in a high-income country. This prospective controlled cohort study showed no clinical effectiveness of vitamin A supplementation in children hospitalized for measles in a setting with low prevalence of malnutrition and vitamin A deficiency.

Measles is currently spreading in several high-income countries in which the infection was expected to be eliminated, according to the WHO elimination plan.[22] Consequences of acute infection may be severe. Approximately 30% of affected children worldwide develop at least one complication. Additionally, 2% die from infection in low-income countries, and <0.1% die in high-income countries.[23] Vitamin A deficiency contributes to the incidence of measles-related complications and increases the risk of death. Furthermore, measles virus infection itself is able to trigger acute vitamin A deficiency and xerophthalmia.[15]

To date, we have no options to treat measles, and the management is limited to supportive care and therapy for secondary bacterial infections. Supplementation of vitamin A during measles reduces the incidence of complications and mortality in low-income countries where malnutrition and vitamin A deficiency are common.[10] In 2017, WHO renewed its recommendation of treating all children with measles with age-specific doses of vitamin A.[11] In addition, WHO extended this recommendation to all cases of severe measles, "also in countries where measles is not usually severe." The American Academy of Pediatrics, as well as the CDC, currently recommend the same intervention for all children with severe infections, including those hospitalized for measles.[12] However, evidence supporting this intervention in high-income countries is very limited, and primarily based on 2 intervention studies. The first was performed in England in 1932, and reported a reduction in complications and mortality in children who received high doses of vitamins A and D. This study includes several risks of bias and because 2 different vitamins were used, the effects of single supplementation are not estimable. The second randomized study, published 20 years ago in Japanese, reported a shorter duration of cough and fever in patients with measles who received a single dose of 100,000 UI of vitamin A, compared with control groups.[16] The risk of bias is difficult to estimate, as the study has not been translated into English and the dose used in that study differs from the one currently recommended by WHO.

In contrast to previous data, the results of the present study did not show any substantial benefits of vitamin A supplementation in children hospitalized for measles in a high-income country. Vitamin A, administered in accordance with WHO recommendations, did not reduce the degree or duration of fever, duration of hospitalization, or rate of complications. Due to the rarity of fatal measles, cases in high-income settings, mortality was not considered as primary outcome in the present study and no fatal cases were recorded during observation. Because malnourished children may benefit from vitamin A supplementation during measles virus infection,[10] we were intended to investigate the difference in clinical outcomes in children with weight-for-age <2 SD at hospital admission. Only few children satisfied this criterion, and only one received vitamin A, hence this analysis cannot lead to conclusive results.

Overall hematologic complications that affected about half of the study population, were slightly reduced in children who received vitamin A, although this difference reached statistical significance only in children under the age of 2 years. However, as rates of hematologic complications vary by measles genotype,[8] and genotype distribution was not homogeneous in our population, possible changes may not be clearly linked to vitamin A supplementation. Moreover, lymphocytopenia and neutropenia, which were commonly observed, appeared self-limiting

and equally distributed among the groups, and were of minor clinical impact.

As WHO has published alerts regarding the severity of measles in younger children and those with underlying conditions (mainly immune deficiencies), and vitamin A supplementation appeared to be more effective in children below 24 months of age,[24] we tested the hypothesis of different effects in specific subgroups. However, no relevant differences were observed. Similarly, we hypothesized that vitamin A might have a time-related effect. However, in children with known measles exposure who may have more rapid access to care, as well as in those admitted within 48 hours after symptoms onset, primary and secondary outcomes were similarly distributed among the study groups.

For any kind of intervention, medical decisions are based on the balance between clinical efficacy, and adverse events and costs. High doses of vitamin A may occasionally cause headaches, loss of appetite, vomiting, and bulging fontanelles in infants.[25] These side effects are usually mild and self-limiting, and rarely observed. No side effects were observed in our population, as well as in all 8 studies included in the Cochrane meta-analysis.[10]

Costs of vitamin A supplementation may vary according to the setting but are usually very limited. In our study, the cost of vitamin A supplementation was 0.95 euros (about 1.1 USD) for 50,000 UI (1 mL of product), resulting a maximum of 7.5 euros (about 8.2 USD) for any cycle of treatment in older children. In our study, the major "cost" was attributable to the efforts of a drug search on the market. Those costs and potential side effects should be weighed against the lack of clinical efficacy.

The present study has several limitations. First, this was not a randomized placebo-controlled trial. As previously reported, the world's main health authorities recommend vitamin A supplementation for all children admitted to the hospital for severe measles. According to currently available evidence, denial of appropriate treatment to infected children or the allocation of a placebo would have been unethical. However, due to the unpredictable availability of vitamin A at the time of the study, children "randomly" received supplementation during the outbreak. To reduce the impact that seasonal difference may have had on clinical outcomes, cases were matched according to the season of hospitalization during the 43 months of observation.

In addition, due to the end of the measles outbreak in Italy in May 2019, we did not reach the estimated sample size. However, in a recent measles outbreak report in the United States, the CDC reported <10% hospitalization among the 700 cases recorded in 2019.[26] Due to the rarity of measles in high-income setting and the relatively low hospitalization rate, the enrollment of more than 100 inpatients children, resulting in a study power of 80% should be taken into account.

Second, we used an oil-based formulation of vitamin A, which might have had an impact on its effectiveness. Previous data showed a higher impact of water-based formulation on mortality in developing areas.[10] However, an oil-based vitamin A formulation was associated with a reduction in measles-related mortality rates by more than 70% in African children.[27] Furthermore, due to higher stability and lower costs, oil-based formulations are currently recommended by WHO and were the only version available on the Italian market at the time of the present study.

In conclusion, to our knowledge, this is the first English-language study to test the effectiveness of vitamin A in measles-infected children living in a high-income country.

According to the results of this prospective cohort study, the supplementation of vitamin A in treatment for measles does not provide clinical benefits in terms of reduced duration of fever or hospitalization, rate of complications or need for antibiotic treatment. These results call for further prospective studies in larger populations living in high-income settings. Due to current authorities' recommendations, the unpredictability of new outbreaks and, hopefully, a return to appropriate immunization coverage, randomized controlled trials may be difficult to carry out in this setting, and its appropriateness might be questionable also considering the good vitamin A safety profile. However, in the current scenario characterized by possible further measles cases in high-income settings, we would not be concerned if vitamin A was not readily available.

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