Translational Research on vitamin A: from randomized trial to intervention and impact assessment

Pesquisa Translacional em vitamina A: do ensaio randomizado à intervenção e à avaliação do impacto

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ABSTRACT Translational Research is interdisciplinary and supported by three pillars: bench (basic investigation), bedside (clinical applications) and community (applications in healthcare systems). The study, based on the five stages of translational research, reviewed the history of vitamin A deficiency and nutritional blindness in Brazil (T0); the pathway from scientific discovery to intervention choice – vitamin supplementation (T1); an assessment of the candidate intervention efficacy via randomized controlled trial (T2); the assessment of implementation and coverage in practice (T3) and the intervention impact assessment (T4). To estimate the impact, we applied Wald superior statistics to identify structural breaks along the time series of general mortality of children between 6 and 59 months of age. In the Northeast, region that presents the largest program coverage, the model pointed to three breaks: August/1984, June/1994 and May/2006, in which we estimated reductions of 10%, 17% and 23%, respectively, in the monthly incidence of children´s death. The process to construct knowledge about vitamin A deficiency, the choice of the intervention, the knowledge translation to establish the National Vitamin A Supplementation Program and the evaluation of its impact, constitute an example of translational research in collective health.

KEYWORDS Translational medical research. Vitamin A deficiency. Health impact assessment.

RESUMO *A Pesquisa Translacional é interdisciplinar e está apoiada em três pilares: pesquisa de bancada (básica), leito (aplicações clínicas) e comunidade (aplicações nos sistemas de saúde). O estudo, baseado nos cinco estágios da Pesquisa Translacional, resgatou o histórico da deficiência de vitamina A e da cegueira nutricional no Brasil (T0); o caminho da descoberta científica à escolha da intervenção – suplementação vitamínica (T1); a avaliação da eficácia da intervenção candidata por ensaio randomizado e controlado (T2); a avaliação da implementação e da cobertura na prática (T3); e a avaliação do impacto da intervenção (T4). Para verificar o impacto, aplicou-se a estatística superior de Wald, visando identificar quebras estruturais ao longo da série histórica da mortalidade geral de crianças entre 6 e 59 meses de idade. Para a região Nordeste, que apresentou a maior cobertura programática, o modelo sinalizou três quebras – agosto/1984, junho/1994 e maio/2006 –, nas quais foram estimadas reduções de 10%, 17% e 23%, respectivamente, na ocorrência*

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mensal de óbitos infantis. O processo para a construção do conhecimento sobre a deficiência desta vitamina, a escolha da intervenção, a aplicação deste conhecimento no estabelecimento do Programa Nacional de Suplementação de Vitamina A e a avaliação do seu impacto configuram um exemplo de Pesquisa Translacional em saúde coletiva.

PALAVRAS-CHAVE *Pesquisa médica translacional. Deficiência de vitamina A. Avaliação do impacto na saúde.*

Introduction

Translational Research (TR) is an interdisciplinary branch of biomedical investigation supported by three pillars: bench investigation (basic), bedside (clinical applications), and community (applications in healthcare systems). Its goal is to coalesce disciplines, resources, expertise, and techniques to promote enhancements in prevention, diagnosis, and therapies with the purpose of improving the global healthcare system[1]. At first glance, the concept seems so obvious that one may ask why only now is TR drawing the attention of health policy managers[2].

Some researchers propose five stages for TR (from T0 to T4) and they highlight the role of epidemiology in the translation of scientific discoveries into population's health impacts[3]. Epidemiology quantifies and integrates knowledge among disciplines, as well as provides methods and tools; as a consequence, it has applications in all stages of TR. Epidemiology is useful in T0, in the description of disease occurrence according to agent, host and environment, and in the identification of health determinants in surveys, case-control and cohort studies.

The following stage involves scientific discovery and the development of applications on health, using clinical and populational studies (T1). Next, epidemiology contributes to evaluate the efficacy of candidate interventions, using randomized controlled trials (T2). Subsequently, epidemiology analyses facilitators and barriers to the implementation of the candidate intervention (T3). Finally, epidemiology can evaluate the impact of interventions on health indicators, using observational or quasi-experimental methods (T4). Epidemiology also plays an important role in the syntheses of evidences, especially by using quantitative methods, as in systematic reviews and meta-analysis[3], essential in evidence-based decision-making.

Vitamin A Deficiency (VAD), or hypovitaminosis A, constitutes a nutritional problem with wide geographic distribution, especially in developing countries, and corresponds to the subclinical vitamin A deficiency conditions. The term 'xerophthalmia' is the designation of the spectrum of signs and symptoms attributed to this deficiency that includes Bitot's spots in the conjunctiva and night blindness (reversible)[4] and permanent blindness, when ocular structures are destroyed[5,6]. The detailed description of corneal lesions that result in irreversible blindness and its nutritional origin was first registered in the scientific literature by the Brazilian medical doctor Manoel da Gama Lobo, in 1864, in slave children in Rio de Janeiro. Fifty years before the discovery of vitamins, Lobo[5] predicted: "[...] the body, lacking vital principles, cannot provide the necessary principles for the nutrition of the cornea". It was only in 1913 that McCollum and Davis characterized the essential nutrient 'liposoluble factor A', later named vitamin A[7].

Research directed to the description and control of VAD and nutritional blindness was conducted in Brazil during recent decades by authors of this paper (LMPS, ASD, MCM, MLB). The aim of this study is to describe Translational Research on vitamin A in an orderly manner, according to TR stages, including: VAD prevalence, pathway from the scientific discovery to the intervention choice, syntheses of evidence, assessment of the candidate intervention efficacy, assessment of the implementation and intervention coverage in practice, and assessment of the intervention impact on health. It is the report of a Translational Research in public health, performed by authors of this study, before the definition of TR, as such, in the scientific literature.

Methods

This is a quali-quantative study with a descriptive and analytical design. The research carried out a documental search for scientific papers and publications on VAD and strategies for its control in Brazil; they were analyzed, organized and presented according to TR stages from T0 to T3.

On stage T4, an analytical quantitative study was performed by means of econometric techniques to assess the intervention impact. The exposition to the intervention was characterized using secondary data on the quantity of doses and coverage of vitamin A supplementation from 1983 to 2018, in all states of Brazil, obtained from official reports of the Ministry of Health (MOH).

To evaluate the impact on health indicators, the research used the strategy published by Piehl[8], which seeks to detect structural changes related to public policies. Wald[9,10] superior statistics was applied to identify structural breaks along the time series of the outcome indicator, which was the general mortality of children between 6 and 59 months of age. However, the existence of a structural break of the parameters is not a proof that the impact has been caused by the intervention, so it is necessary to perform additional analyses. Therefore, given the nature of deaths enumeration data, the Poisson regression model was used to measure the effects[11].

As the exact moment of any of the program's effects cannot be determined, the method has conditioned Wald superior statistics to 'date windows' between the beginning of the intervention and the maturation of outcomes[8]. In the case of vitamin A, the program has different implementation phases, enabling the identification of different 'date windows' to assess possible data discontinuity.

Mortality data follow a monthly periodicity, covering from January 1979 to December 2017. General children mortality data, from 6 to 59 months of age, are made available by the MOH Mortality Data System (Sistema de Informação sobre Mortalidade – SIM/Datasus). The control variables for the Poisson regression model were as follows: *per capita* income, binary indicator of economic crisis (for periods when real variation of the Gross Domestic Product – GDP was negative), and poor population rate (variables obtained from the Brazilian Institute of Geography and Statistics – IBGE). Besides socioeconomic factors, the study used the number of physicians per 1,000 inhabitants, extracted from the governmental annual social data report (Relação Anual de Informações Sociais – Rais), and the number of deaths of children with less than one month of life (as an alternative counterfactual scenario of deaths tendency). The study used public secondary data and therefore was exempted from Ethics Committee approval.

Results and discussion

Chart 1 gathers historical publications related to VAD and nutritional blindness[4-7,12-17]. The oldest mention to night blindness was found on the Ebers Papyrus (circa 1600 BC) with the indication of ox liver (currently recognized as rich in vitamin A) for the cure of night blindness caused by VAD[4]. After the initial findings by Gama Lobo in Brazil in 1864[5,6], there were reports on hypovitaminosis A and xerophthalmia, e.g. the occurrence in Rio de Janeiro in 1883[12], in the Northeast in 1902[13], 1934[14], 1946[15], 1958[16], and in Florianopolis in 1966[17]. More recent publications related to T0 through T4 stages of the TR will be presented in sequence.

Chart 1. Timeline presentation of main articles and publications on Vitamin A Deficiency (VAD) and nutritional blindness according to the Translational Research stages. Brazil, 1865 and 2019

Translational Research stages	Date of studies	Description of article or publication (date of publication)	Reference
Historical publications on vitamin A and nutritional blindness	1600 BC	Ebers Papyrus: indicates ox liver for the cure of night blindness, an initial VAD symptom – apud Wolf (1978)	04
	1865	Gama Lobo: describes *'ophthalmia brasiliana'* in slave children in RJ and attributes the new ophthalmia to malnutrition (1865/6)	05 / 06
	1883	Hilário de Gouvêa: reaffirms the nutritional origin of *'ophthalmia brasiliana'* (1883)	12
	1902	Euclydes da Cunha: describes the occurrence of night blindness during drought in Northeast in 'Os Sertões' (1902)	13
	1913	McCollum: discovers and characterizes vitamin A as essential nutrient and preventive factor of night blindness (1967)	07
	1934	Robalinho Cavalcanti: child blindness in the ophthalmologic services in Ceará (1934)	14
	1946	Josué de Castro: 'The Geography of Hunger' ('Geografia da Fome') (1946)	15
	1958	Leão: describes malnutrition and vitamin A deficiency among schools in Fortaleza, Ceará (1958)	16
	1966	Pereira, Freusberg: nutritional blindness in 66 children with intake of skim milk from Unicef in Florianópolis, SC (1966)	17
T0 Description and observational studies	1981-2	Santos et al.: epidemiological survey with 7,862 children in the 3 mesoregions of Paraíba; Bitot's spots prevalence (1983)	18
	1981-4	D'Ans et al.: epidemiological survey with 5,426 children in 11 microregions of Paraíba; Bitot's spots prevalence (1988)	19
	1982-4	Araújo et al.: surveillance at University Hospital of João Pessoa, Paraíba: nutritional blindness in children 0-2 years (1984)	20
	1984	Flores & Araújo: low liver concentration of retinol in children's autopsies in Pernambuco (1984)	22
	1984	Flores et al.: low serum levels of retinol in pre-school children in Pernambuco (1984)	23
	1986	Mariath at al.: survey with 6,291 children in Sertão of Rio Grande Norte; clinical cases and Bitot's spots (1989)	21
	1989	Santos et al.: survey with 754 children in Sertão of Bahia: inadequate intake and low serum levels of retinol (1996)	24
T1 From discovery to application and intervention choice	1982-1984	Sommer et al.: first controlled trial with vitamin A; indicated reduction of 34% in children mortality in Indonesia (1986)	26
	1994	Brasil/ Inan: Portaria nr 2160, 23/12/1994, National Program of Vitamin A Deficiency Control (1994) (extinguished in 1997)	32
	2005	Brasil/ MS: Portaria nr 729, 13/05/2005, reestablishes National Program of Vitamin A Supplementation (PNSVA) (2005 to date)	33

Chart 1. (cont.)

T2 From application to synthesis of evidences	1986-1992	Fawzi et al.: meta-analysis of 12 controlled trials; estimated 30% reduction in children mortality (1993)	34
	1986-1992	Glauziou, Makerras: meta-analysis of 20 controlled trials; estimated 30% reduction in children mortality (1993)	35
	1986-1992	Tonascia: meta-analysis of six controlled trials; estimated 34% reduction in children mortality (1993)	36
	1986-1993	Beaton et al.: meta-analysis of eight controlled trials; estimated 23% reduction in children mortality (1994)	37
From application to efficacy assessment	1991	Barreto et al.: randomized controlled study in children from 24 to 36 months in Sertão of Bahia, indicated 6% reduction in diarrhea cases incidence, 9% in moderate diarrhea incidence, and 20% in severe diarrhea incidence (1994)	38
T3 From recommendation to assessment of implementation and coverage	1983-2003	Martins et al.: describes the pathway of actions implementation of vitamin A deficiency control in Brazil (2007)	25
	1995-2002	Martins et al.: assesses the implementation of the national program of combat against vitamin A deficiency in Bahia (2007)	39
	2017	Brasil/ MS/ NT 175/ 2018: publicization of the coverage of the National Program of Vitamin A Supplementation in 2017 (2018)	40
	2008	Almeida et al.: low rate of knowledge on the program and vitamin A, Cabedelo, Paraíba (2010)	42
	2012	Marques et al.: practices and social representation of mothers on VAD, municipality of Vale do Jequitinhonha, Minas Gerais (2017)	43
	2014	Lima et al.: little knowledge on the program and on vitamin A, in a population-based sample, Alagoas (2018)	44
	2007	Paiva et al.: analyses the view of the family health team on the vitamin A supplementation program, Paraíba (2011)	45
	2010	Brito et al.: perception of health professionals on the vitamin A supplementation program, Campina Grande, Paraíba (2016)	46
T4 From practice to impact assessment	1984-2017	Santos et al.: Translational Research on vitamin A: from randomized trial to intervention and impact assessment; indicated 'structural breaks' with 10% reduction in 1984, 17% in 1994 and 23% in 2006 in children mortality in the Northeast (2019)	Present study

Source: Own elaboration.

T0 – Description and observational studies

Observational studies on VAD and nutritional blindness prevalence in the Northeast region of Brazil, carried out from 1980 to 1994, comprise the initial stage (T0) of this TR (1994 is the limit year for being the date of the official intervention choice by the Ministry of Health). A considerable number of those studies were the result of field work of two authors of this paper, who at that time worked at the Federal University of Paraíba (LMPS, ASD). Worthy of note is the nutritional clinical study by Santos et al.[18] involving 7,862 children in the three bioclimatic meso-regions of the state of Paraíba, which registered Bitot's spots prevalence, indicative of VAD as a public health problem, in the remote areas known as *sertão*, in 1981-1982. The same research group documented clinical manifestations of moderate xerophthalmia, as well as cicatricial sequalae, in 5,426 children in Paraíba between 1981 and 1984[19]. As from 1982, the group's ophthalmologist (ASD) established a xerophthalmia surveillance system at the pediatrics service of the University Hospital of João Pessoa, in the capital of Paraíba, and several cases of acute ocular lesions, with corneal destruction and nutritional blindness, were diagnosed, treated and photographed[20]. In 1986, the same research group observed clinical evidences of moderate xerophthalmia (Bitot's spots) in the *sertão* of the state of Rio Grande do Norte[21]. In the state of Pernambuco, as from the 1980s, researchers documented biochemical evidences of VAD, observed both from the low concentration of liver reserves[22] and from the low serum levels of retinol in preschool children[23]. In 1989 a group of authors of this paper, then at the Federal University of Bahia (LMPS, MLB, MCM), conducted a field research in seven municipalities of the semiarid region of the state of Bahia, and reported a high prevalence of inadequate serum levels of retinol and low intake of food source of vitamin A[24].

These observational studies, carried out in the 1980s (*chart 1*, T0), provided more robust evidences for MOH decision-making on the recognition of VAD as a significant public health problem in the semiarid region of Brazil (north of the state of Minas Gerais and all Northeast region of the country) and, thus, to initiate vitamin A supplementation with the purpose of preventing nutritional blindness[25].

T1 – From scientific discovery to health application and intervention choice

The most relevant scientific discovery was the effect of vitamin A supplementation on child mortality[26]. Until the 1980s vitamin A deficiency studies focused on ocular manifestations resulting from the deficiency condition, virtually ignoring possible systemic benefits. The seminal study conducted by Alfred Sommer and collaborators was the first controlled trial with vitamin A supplementation, every six months, on 25,939 pre-school children in Indonesia. Outcomes indicated a 34% mortality decrease among children of the intervention group (vitamin A) compared to the control group[26]. Since then, there have been investigations with the purpose of assessing the role of vitamin A deficiency in the prevention of child morbimortality. Between 1982 and 1994, observational studies and randomized controlled clinical trials conducted in Indonesia, India and Sudan reported that vitamin A supplementation significantly reduced children death risk, an effect that reached up to 54% (RR=0.46)[26-29]. However, another study in Sudan observed that vitamin A supplementation failed in decreasing mortally risk[30,31].

Even though the National Food Institute (Instituto Nacional de Alimentação – Inan), an autonomous agency linked to the MOH, had started vitamin A supplementation in 1983 with the aim of preventing nutritional blindness in the country's Northeastern states, the National Program was actually created in 1994. Consultations with international and national experts, among which one author of this paper (LMPS), and the evidence available at the time, grounded the decision made by INAN to publish Ordinance nr 2160 of December 23, 1994 creating the National Program of Control of Vitamin A Deficiencies (Programa Nacional de Controle das Deficiências de Vitamina A)[32]. Among the strategies of the Program, there was the massive distribution of vitamin A megadoses to children from 6 to 59 months of age in the endemic areas, in collaboration with the National Immunization Program (Programa Nacional de Imunização – PNI), besides countrywide VAD mapping and studies on the feasibility of fortifying mass consumption food with vitamin A (*chart 1*, T1).

However, the extinction of INAN in July 1997 implied the automatic cancellation of Ordinance nr 2160. Only eight years later, Ordinance nr 729 of May 13, 2005 was signed, reinstating the National Program on Vitamin A Supplementation (Programa Nacional de Suplementação de Vitamina A – PNSVA), in force to date[33]. The attributions defined for MOH include: (I) purchase and forwarding of vitamin A supplement; (II) follow-up and monitoring the situation of states and municipalities regarding the level of implementation and operationalization of the Program and population coverage; (III) assessment of the performance and impact of the Program on national level, and support to actions of the same nature in states and municipalities (*chart 1*, T1).

T2 – From application to syntheses of evidence and assessment of intervention efficacy

As previously mentioned, controlled randomized trials performed between 1982 and 1994 in Indonesia, India and Sudan indicated that vitamin A supplementation significantly reduced children death risk[26-29]. However, a study in Sudan[30,31] observed different outcomes. Due to this controversy, and considering the relevance of the theme, four meta-analyses were developed; the conclusions pointed to a protective effect of vitamin A. Two meta-analyses indicated 30% reduction of child mortality[34,35] and a third one 34%[36]. The fourth study indicated that vitamin A supplementation reduced mortality by 23%[37]; the effect on the reduction of child mortality rates was observed even in localities where there was a low prevalence of xerophthalmia. However, it was not possible to derive conclusions for children in the age group under six months, and in places where hypovitaminosis A was verified through biochemical analysis, but without clinical manifestations. Researchers alerted to the possibility that the effect may not exist in populations with low child mortality rates[37] (*chart 1*, T2).

At this stage, the efficacy of the candidate intervention was assessed in Brazil. In the beginning of the 1990s, authors of this paper (MLB, LMPS, MCM) conducted a randomized, double-blind, placebo-controlled study in the semiarid region of Bahia. The aim was to assess the efficacy of vitamin A supplementation on child morbidity, especially diarrhea and acute respiratory infection[38]. The results showed a small but significant reduction of 6% in the overall incidence of diarrhea (RR=0.94 $IC_{95\%}$ 0.90-0.98). However, when the analysis was on severe diarrhea, assessed from the frequency of liquid or semiliquid defecation in 24 hours, supplementation resulted in a reduction of 9% in the incidence of moderate diarrhea episodes (RR=0.91, $IC_{95\%}$ 0.85-0.98) and of 20% in severe diarrhea cases (RR=0.80 $IC_{95\%}$ 0.65-0.98)[38]. The study also showed a reduction of the average daily prevalence of diarrhea, *pari passu* to the number of more severe episodes, with four, five, six, or more dejections in 24 hours. The prevalence ratios in supplemented and placebo children were 0.90, 0.80 and 0.77, respectively. No effect was observed regarding respiratory infections[38] (*chart 1*, T2).

T3 – Assessment of intervention implementation

In general, there are scarce systematic actions of implementation assessment as instrument of support to management, aiming at the improvement of the decision-making process in collective health. Implementation research, to study this intervention in practice, was carried out by authors of this paper (MCM, LMPS)[25,39]. The logistics of vitamin A capsules purchase is centralized at the MOH. Until 2000, Brazil was dependent on capsules donation from international agencies, resulting in logistic problems of distribution to municipalities[25]. As from 2001, the MOH started to purchase vitamin A capsules directly from the Pharmaceutical Technology Institute of Oswaldo Cruz Foundation (Farmanguinhos/Fiocruz), seeking to guarantee stability to the purchase process[25]. According to a 2018 Technical Note of the MOH, despite the direct purchase of capsules, there remains irregularities in the supply to municipalities[40].

The management of the distribution chain of capsules is under the responsibility of all three governmental levels – federal, state, and municipal. Therefore, hindrances at any of these spheres result in losses in the process of distribution of the supplement to the target population. Brazil has pioneered the strategy of distribution of vitamin A integrated to immunization (PNI), being this the main strategy during several years, especially in the Northeast region, constituting an important component to help achieving the Millennium Development Goals for child health[25].

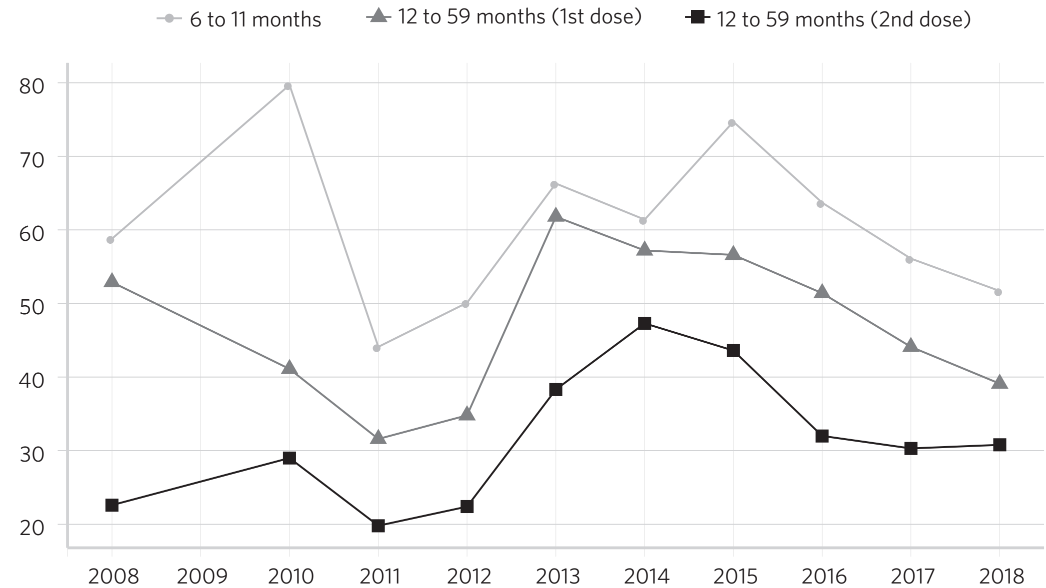
Presently, MOH recommends that vitamin A supplementation is carried out mainly in the routine of healthcare services, and when necessary complementary strategies should be adopted[41]. During the period 2010-2018, routine healthcare services contributed to approximately 90% of the annual distribution of vitamin A capsules to children between 6 and 59 months of age.

The stimulus to vitamin A supplementation in the routine services makes feasible the interaction of the child's family with the local healthcare team, enabling health professionals to provide orientation about the deficiency of this vitamin and stimulate the practice of healthy food intake, besides verifying the regularity of supplementation[41]. Although healthcare services are the main distribution channel of vitamin A supplementation, the knowledge about the Program has not been detected by studies that assessed the degree of information of beneficiaries about the Program and this vitamin[39,42-44], as well as studies that analyzed the capacitation level of PNSVA professionals[43,45,46].

The average coverage rate for children between 6 and 59 months of age in the period 1994-2000, during which the country depended on international donations of vitamin A capsules, was approximately 40%[25]. The coverage remained very low (44%) in 2001, the year of transition in the process of capsules purchase. However, in 2002 and 2003 the percentages of coverage were 72% and 68%, respectively[25]. Internal data of MOH (not publicized) demonstrate that coverage during 2005, 2006 and 2007 for children of 6 to 11 months of age, and 12 to 59 months of age, were respectively: 77.4% and 50.2%; 73.0% and 43.3%; 79.1% and 39.4%.

The average coverage in the last ten years (2008-2018 – data not available for 2009) was 60.7%, 47.1% and 31.6% for children from 6 to 11 months of age, first dose and second dose for children from 12 to 59 months of age, respectively (*graph 1*). Considering the coverage for children from 6 to 11 months, and the coverage of the first dose for children from 12 to 59 months, there has been an increase in relation to the average of the period 1994-2000. However, it is observed that the total coverage remains not very expressive, especially regarding the coverage of the second dose for children from 12 to 59 months of age.

Graph 1. Coverage (%) of vitamin A capsules distribution to children 6 to 59 months of age during the period 2008-2018



Age group (months)	2008	2010	2011	2012	2013	2014	2015	2016	2017	2018
6 to 11	58.8	79.7	44.1	50.1	66.3	61.4	74.7	63.7	56.1	51.7
12 to 59 (1st dose)	52.9	41.1	31.6	34.8	61.8	57.2	56.6	51.4	44.1	39.1
12 to 59 (2nd dose)	22.6	29.0	19.8	22.4	38.3	47.3	43.6	32.0	30.3	30.8

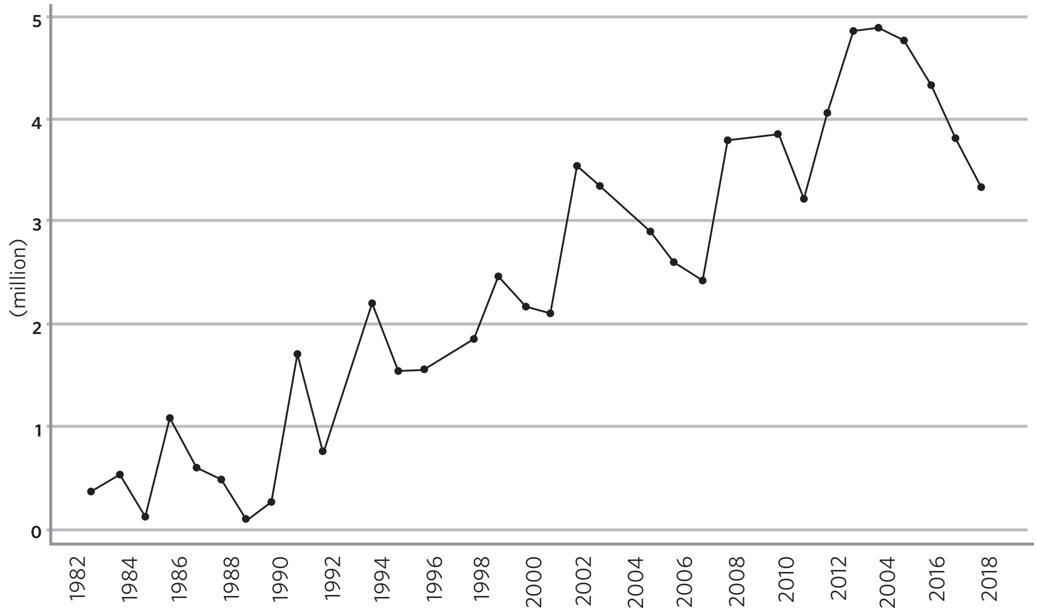
Source: 2009 data not available; 2008 and 2010 internal data Ministry of Health; 2011-2018 data available at Ministry of Health system <http://dab.saude.gov.br/portaldab/ape_vitamina_a.php> [access on Feb. 23, 2019].

It is observed that there is a maintenance of a higher, but not adequate, coverage pattern for children from 6 to 11 months of age, in comparison with the coverage pattern in older children, as reported by Martins[25]. This is an interesting aspect, because it provides vitamin A protection precisely to one of the groups that is biologically most vulnerable to morbidity from infections. Probably, this higher coverage is due to routine contacts with the primary healthcare services, such as immunization and follow-up for growth/development of children in this age group[25].

It is important to underline that in 2010 the Program was extended to the municipalities that comprise the Legal Amazon region and to Special Indigenous Sanitary Districts; and in 2012 the Program had its coverage extended to attend the new demand of the Action Kind Brazil (Ação Brasil Carinhoso) included in the Plan Brazil Without Misery (Plano Brasil Sem Miséria). Consequently, there has been an increase in the quantity of vitamin A capsules distributed through the country (*graph 2*), especially in the period 2013-2015. On the other hand, a tendency of decline is observed both on the quantity of supplement distributed as from 2016 (*graph 2*) and on the coverage of the Program (*graph 1*).

In sum, it can be observed that VAD control actions have been expanded and strengthened in Brazil. However, evidence points to the need of urgent strategies to improve the quality of the implementation, services supply and coverage of PNSVA.

Graph 2. Quantity of vitamin A capsules (in million) administered to children from 6 to 59 months of age during the period 1983-2018



Year	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1994	1995	1996	1998	1999	2000
Capsules	0.38	0.55	0.13	1.09	0.60	0.49	0.11	0.28	1.72	0.75	2.22	1.55	1.55	1.86	2.48	2.18
Year	**2001**	**2002**	**2003**	**2005**	**2006**	**2007**	**2008**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
Capsules	2.13	3.55	3.35	2.91	2.57	2.44	3.80	3.86	3.22	4.06	4.88	4.90	4.78	4.34	3.81	3.33

Source: 1983 to 2003 Brasil[39]; 2005-2008, 2010 internal data Ministry of Health; 2011 to 2018 data available at: <http://dab.saude.gov.br/portaldab/ape_vitamina_a.php> [access on Feb. 23, 2019]; 1993, 1997, 2004 and 2009 data not available.

T4 – From practice to impact evaluation in health

This stage aimed at assessing the intervention impact on the population's health. The intervention under analysis brings specific challenges to its assessment, since vitamin A deficiency control started in 1983 in areas of the states of Paraíba, Pernambuco and Minas Gerais, with important changes occurring along time until the creation of PNSVA in 2005. It should be stressed that this intervention, already in the first year, distributed 384,420 megadoses of vitamin A in areas with high socioeconomic vulnerability[25] and, therefore, this could have been verified in health indicators.

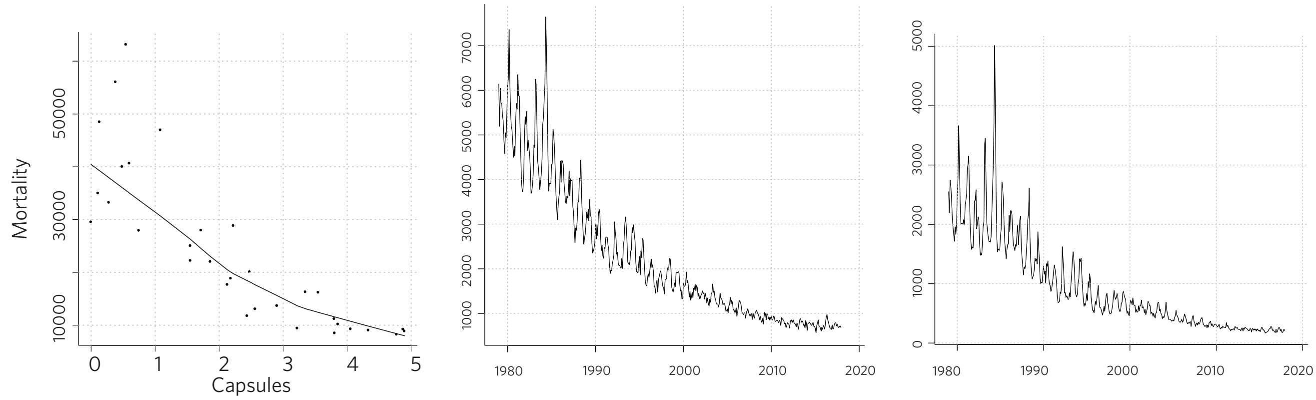
Figure 1 shows a general description of data on pre-school children mortality, with a highlight on the first panel to the association between the distribution of vitamin A capsules and mortality level, while the other panels show the time series of mortality for Brazil and the Northeast region. *Figure 1*a shows a strong negative correlation (Pearson coefficient -84, with p-value=0.00) between the distribution of vitamin A capsules and the mortality of children in the age group from 6 to 59 months of age in the period 1983 to 2017. Furthermore, *figures 1b* and *1c* evidence a mortality reduction tendency in the age group under study during four decades, although it shows stabilization in the last years.

Figure 1. General children mortality between 6 and 59 months of age in Brazil and in the Northeast region from 1979 to 2017

(a) Brazil: Vitamin A (in millions of capsules) *versus* Mortality, 1983-2017

(b) Brazil: Mortality in a monthly time series 1979-2017

(c) Northeast: Mortality in a monthly time series 1979-2017



Pearson correlation coefficient: -0,84 (p-value=0,00)
Line of adjusted tendency by a local polynomial regression.

Source: Data on vitamin A supplementation from 1983 to 2003 Martins[38]; 2004 to 2017 data from Ministry of Health available at <http://dab.saude.gov.br/portaldab/ape_vitamina_a.php> [access on Feb 23, 2019]; data on mortality from microdata of SIM/Datasus.

A central point in this assessment is to identify how much of the reduction of obits observed could be attributed to vitamin A supplementation. Therefore, at this stage the research performed structural breaks trials in the time series of obits between 6 and 59 months of age using Wald[9] superior statistics, together with windows of dates and control variables[8], to identify discontinuities and the effects of vitamin A distribution drawing on Poisson regression model. For this purpose, three intervals were defined for the application of Wald statistics: 1983 (initial implementation), 1994 (restructuring) and 2005 (PNSVA creation), with a window of up to 36 months in each case (given the periodicity of the distribution of megadoses to children every six months). Considering that the Northeast region, given its social and economic vulnerability, has been from the start of the program a central target of the action, specific estimates were made for this regional scope.

Table 1 reports the outcomes of the search for maximum structural break (Wald superior statistics) at each of the aforementioned intervals, in which Wald statistics exceeds the asymptotic critical values on the level of significance of 1%. Thus, in the model for Brazil two structural breaks were identified (occurring in August 1984 and April 1995), whereas in the model for the Northeast region three breaks were observed (August 1984, June 1994, and May 2006).

Table 1. Outcomes of the assessment model of vitamin A impacts on general mortality among children from 6 to 59 months of age, 1979 to 2017

Scope	Identified breaks	Wald Superior Statistics	Effect	Lower Limit	Upper Limit
Brazil	August, 1984	48.9	-6.7%*	-7.6%	-5.6%
	April, 1995	47.1	-27.6%*	-27.7%	-27.5%
Northeast	August, 1984	45.3	-10.2%*	-10.9%	-9.6%
	June, 1994	33.8	-17.0%*	-17.2%	-16.8%
	May, 2006	18.2	-23.2%*	-23.6%	-22.8%

Source: Own elaboration.

*p-value<1%.

Notes: Number of observations = 468 months, from January 1979 to December 2017. Inferior and superior limits with 95% reliability. All models used control variables for *per capita* income, economic crisis, poverty, density of physicians and alternative counterfactual of obits tendency of younger than one month of life.

The identified effects on mortality depend on the window of dates referring to the stage of implementation of the program, stressing that in all of the presented scenarios the parameters are statistically significant at 1%. In August 1984, one year after the start of the supplementation, the estimate was a reduction of -6.7% on the monthly level of obits between 6 and 59 months of age for Brazil, and above -10% in the Northeast, the region that most benefited from the program in the period. On the second cycle of implementation, with the expansion of the program coverage, the discontinuity related to the supplementation in April 1995 resulted in an effect of -27.6% for the level of Brazil, whereas in the Northeast the estimate was of -17%. Finally, the third break associated to the program appeared as statistically significant only for the group of children in the Northeast region, with an effect close to -23% in mortality, one year after the instauration of PNSVA. All estimates associated to the effects of the program in Brazil follow the same direction of the impacts observed regarding child mortality in other studies[26-29,34-37]. Considering that public policies and health programs developed in the ambit of SUS are not carried out in an experimental manner and in many cases do not have detailed data on control variables, impact indicators, and coverage evolution of the intervention over individuals and territories attended, the methodological possibilities for impact assessment are considerably restricted.

In this scenario, one of the strong points of the model proposed by Piehl et al.[8], especially in the case of health program analysis, is that it requires a set of data with less informational contents, enabling managers and society to know about the effectiveness of public resources allocated in the area. Therefore, this approach could be used to identify causal effects or those potentially related with any intervention in the health area, as long as there are time series, especially with high time-frequency, about impact indicators, confusion factors, and definitions about the periods of the intervention.

One should be alert to the fact that, as it happens with other techniques to assess non-experimental interventions, estimates of the program's impact should be taken cautiously, because in the model there may exist omitted factors that are not controllable. Hence the recommendation to use an alternative counterfactual scenario to mitigate possible biases in the estimates. In this research, this scenario was developed with the mortality of children younger than one month of life.

The periodic vitamin A supplementation of children from 6 to 59 months of age has been recommended by the World Health Organization (WHO) as a strategy for the prevention and control of hypovitaminosis A in populations in which vitamin A constitutes a public health problem[47]. This strategy has been implemented in over one hundred countries and has presented a significant impact on the reduction (12% to 30%) of child mortality[48]. However, the effect of supplementation has been reevaluated drawing on evidences consubstantiated on analysis of clinical, randomized, and controlled trials performed more recently. It is likely that a significant effect on mortality and morbidity reduction would have been conditioned by some contextual peculiarities of each locality in which the intervention is implemented, and this would modulate the impact. In this sense, the potential beneficial effect of vitamin A supplementation for mortality reduction would occur in areas where the prevalence of maternal hypovitaminosis A constitutes a moderate or severe public health problem, and with high levels of child mortality[49].

Vitamin A is fundamental to the maintenance of the integrity of epithelia, such as those covering the cornea and gastrointestinal and respiratory tracts. There is yet no clear indication of the biological mechanisms by which vitamin A affects mortality. One of the plausible links to explain this effect would be due to the anti-inflammatory and antioxidant action of vitamin A, preserving the defenses of the intestinal tract against infections[50-52]. To this should be added the register of a substantial number of conflicting findings in individual studies conducted in contexts with potential variations in the levels of maternal vitamin A deficiency and child mortality[49], besides the absence of continuity studies to monitor, on the long term, post-supplementation bulging fontanelle. Additional researches are salutary to restructure current policies, evaluating different doses and mechanisms of supplement dispensation. However, it should be stressed that the search of further empirical evidences that could clarify the role of vitamin A in child mortality presents significant limitations, considering that, based on currently available evidences, it would be anti-ethical to develop placebo-controlled trials within populations with verified vitamin A deficiency[48]. Therefore, under the circumstances, it is important to discuss the use of observational or quasi-experimental methods that do not present the limitations of experimental studies.

Conclusions

Translational Research aims to promote the incorporation of research outcomes to achieve enhancements in prevention, diagnosis and treatment for improving population health – a goal pursued by health policies managers[2]. One of the reasons for the distance between basic research and its applications may be the increasing compartmentalization of science. Basic research, which seeks to discover the underlying principles of the natural world, is fundamentally distinct from applied research, which seeks to discover manners of influencing or controlling the world. Basic and applied researchers differ not only in relation to training and tools they bring along to resolve research problems, but also regarding the manner in which they plan the process of research on health.

The distribution of vitamin A capsules in Brazil occurs since 1983; however, studies still detect the prevalence of VAD in some Brazilian states. This fact reinforces the need and the importance of evaluating potentialities and fragilities in the implementation of PNSVA, considering the scarcity of studies to assess the program. This study constitutes the first attempt to evaluate the impact of PNSVA on the indicators of mortality in the population from 6 to 59 months of age.

Collaborators

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