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Homeopathic medicines for prevention of influenza and acute respiratory tract infections in children: blind, randomized, placebo-controlled clinical trial

Camila Monteiro Siqueira^{1,2}, Fortune Homsani¹, Venício Féo da Veiga³, Carlos Lyrio⁴, Haroldo Mattos⁵, Sonia Regina Lambert Passos⁶, José Nelson Couceiro³ and Carla Holandino Quaresma^{1,*}

¹*Departamento de Medicamentos-Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*

²*Instituto Federal do Rio de Janeiro, Rio de Janeiro, Brazil*

³*Instituto de Microbiologia Professor Paulo de Góes, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*

⁴*Instituto Roberto Costa, Rio de Janeiro, Brazil*

⁵*Instituto Evandro Chagas, Rio de Janeiro, Brazil*

⁶*Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil*

Background: Influenza and its complications are common at all ages, especially in children. Vaccines and anti-influenza drugs aim to prevent it. Preventative approaches with favorable risk profiles should be considered for flu, particularly since the evidence of the efficacy of anti-viral drugs is debated.

Methods: This pragmatic clinical trial was conducted in the Brazilian Public Health System in Petrópolis (BPHSP) with children aged from 1 to 5 years old. The medications used were mainly selected based on *in vitro* experiments (InfluBio), and in successful qualitative clinical experiences (Homeopathic Complex). Following informed parental consent, subjects were randomly distributed, in a blind manner, to three experimental groups: Homeopathic Complex, Placebo, and InfluBio. BPHSP health agents collected flu and acute respiratory infection symptomatic episodes monthly following the established protocol. The number of these episodes was registered in one year (2009–2010).

Results: Out of the 600 children recruited, 445 (74.17%) completed the study (149: Homeopathic complex; 151: Placebo; 145: InfluBio). The number of flu and acute respiratory infection symptomatic episodes detected in this clinical trial was low; however, it was different between homeopathic groups and placebo ($p < 0.001$). In the first year post-intervention, 46/151 (30.5%) of children in the placebo group developed 3 or more flu and acute respiratory infection episodes, while there was no episode in the group of 149 children who used Homeopathic Complex, and only 1 episode in the group of 145 (1%) children who received InfluBio.

Conclusion: These results suggested that the use of homeopathic medicines minimized the number of flu and acute respiratory infection symptomatic episodes in children, signaling that the homeopathic prophylactic potential should be investigated in further studies. *Homeopathy* (2015) ■, 1–7.

Key words: Influenza; Flu; Clinical trial; Homeopathic medicines

*Correspondence: Carla Holandino, Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Faculdade de Farmácia, CCS, Bloco B, Sub Solo, Sala, 011, Ilha do Fundão, 21941-902 Rio de Janeiro, RJ, Brazil.
E-mail: cholandino@gmail.com

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Introduction

Influenza (flu) is a viral disease that affects between 5 and 15% of the world population every year. It is caused by influenza viruses and the main symptoms are: high fever, aching muscles, headache and severe malaise, non-productive cough, sore throat and rhinitis. The virus is transmitted from person to person via saliva, sneezing or droplets. Less frequently it is transmitted by contact with a surface that has the flu virus on it followed by contact with the mouth or nose. Influenza spreads rapidly in seasonal epidemics. Most infected people recover without any medical treatment, but in the very young, the elderly, and immune compromised individuals, influenza infection can lead to severe complications, such as pneumonia and death.^{1,2} Acute respiratory illness is the most common clinical infection in childhood and the most frequent reason for children's visits to the pediatrician.³

The co-circulating H1N1 and H3N2 subtypes of influenza A viruses cause symptoms, such as: cough, breathlessness, fever, and sore throat.^{4,5} These viruses have been the main causal agents of annual flu outbreaks occurring in different regions of the world, resulting in 3–5 million severe cases of the disease and 500,000 deaths per year.¹ Nowadays, there are many drugs that are currently prescribed in the treatment of influenza and acute respiratory infection symptoms, and some of these drugs act as neuraminidase inhibitors (oseltamivir and zanamivir) and M2 inhibitors (rimantadine and amantadine) in the treatment of human flu. Jackson *et al* (2010) did a systematic review to evaluate the prophylactic effect of these drugs, showing positive results; nevertheless, these authors signaled the need for further studies with specific populations, like the elderly and children.⁶ In fact, Shun-Shin verified the existence of a post-exposure prophylaxis when neuraminidase inhibitors were used in pediatric patients. However it is important to evaluate the risk and the possible appearance of resistant virus strains.⁷ Additionally, some studies indicate that the conventional drugs have some adverse effects like headaches, gastrointestinal events, nausea, vomiting and others.^{8,9,10} Worrying aspects of these treatments are the rapid resistance acquired, which has been detected 2–3 days after the start of treatment, and the recommendation of not using them in children, especially because of the absence of published clinical trials done with children.¹¹ Besides, zanamivir is an inhaled dry powder, delivered by a specific device, requiring minimum child autonomy to use this medicine.

Recently, Jefferson & Doshi¹² published a systematic review of anti-influenza drugs, such as oseltamivir and zanamivir, in adults and children for the treatment and prevention of flu, without differences in mortality and complications after the use of such drugs. Besides, the authors detected several methodological shortcomings in clinical trials done with anti-influenza drugs in the last decades, and signaled the importance of full clinical studies to support the use of those drugs for the prevention of flu and its complications, such as pneumonia.¹² Among others, these aspects shall stimulate the development of

new drugs for the treatment of influenza and its complications.

Flu epidemics and pandemics caused by H1N1, H2N2 and H3N2 subtypes of influenza A viruses have been responsible for diseases that take devastating proportions.^{13–16} During the 20th century, four flu pandemics occurred, causing 50 million (Spanish, 1918–19), 2–4 million (Asian, 1956), 1–2 million (Hong-Kong, 1968) and 0.7 million (Russian, 1977–78) estimated deaths. The first flu pandemic in the 21st century, also known as swine flu, had as its etiological agent influenza virus A H1N1 and caused nearly 17,000 deaths.¹⁶ This viral subtype still causes death in some countries.

Homeopathic medicines can be prepared from biological materials containing microorganisms, such as viruses and bacteria. Biotherapies are included in this category as remedies prepared from biological products following homeopathic procedures.¹⁷ These medicines can be used to treat infectious diseases with known etiology.

In Brazil, the homeopathic physician Roberto Costa developed a biotherapy using living infectious microorganisms as etiological agents,¹⁸ called "living nosodes". These clinical results motivated a study, using Roberto Costa's methodology, to verify the *in vitro* effects of a living nosode prepared from infectious influenza A virus (A/Aichi/2/68 H3N2 strain).¹⁹ The results obtained from this *in vitro* study showed that this homeopathic medicine presented a stimulatory effect on J774.G8 macrophage cells, inducing an increase in the release of tumor necrosis factor [TNF- α]. These promising *in vitro* results motivated the present clinical trial, developed from the same subtype of H3N2 influenza virus A (A/Victoria/3/75), and conducted in the Brazilian Public Health System (Rio de Janeiro, Brazil), comprising a significant number of children.

In Brazil, homeopathy was incorporated in the Public Health Service, through the National Policy on Complementary and Integrative Practices of the Health Ministry, published in 2006.²⁰ Since then, several different initiatives have been observed in several Brazilian Public Health Hospitals, including the city of Petrópolis, (Rio de Janeiro state). Petrópolis was one of the first cities in Brazil to implement homeopathy in the Public Health System. These experiences with an homeopathic complex consisting of bacterial strains (*Streptococcus* and *Staphylococcus*) and inactivated influenza virus, as tested in the clinical trial reported in this paper. But were not conducted by methods permitting evaluation of their efficacy. Most of these results are unpublished and were maintained as governmental records. This background motivated this clinical trial, using children from Petrópolis that belong to different public health sets.

The present clinical trial evaluated the prophylactic potential of homeopathy in children (1–5 years old) belonging to families from low economic and social classes who do not have access to the private health system and/or additional health care, at Petrópolis, Rio de Janeiro. Furthermore, Petrópolis is a mountain city with high humidity and low temperatures, climatic characteristics

which cause frequent episodes of flu and respiratory diseases, especially in children.

Considering the promising *in vitro* results obtained from infectious influenza A virus biotherapy¹⁹ and the recurrent health problems involved with flu, especially in children, who should not be submitted to traditional antiviral drugs, we developed a clinical trial to test the efficacy of homeopathic medicines in Brazilian children. In this project, two different homeopathic medicines, both classified as biotherapies, were tested: the first one was a biotherapy prepared from the intact influenza A virus sample (InfluBio); the second was a homeopathic complex traditionally used in Petrópolis for the prevention of acute respiratory infections (Homeopathic Complex). Following informed consent from parents or guardians children were randomly distributed, to three different experimental groups: Homeopathic Complex; Placebo; and InfluBio.

Methods

This study was conducted in Petrópolis, a mountain city in the state of Rio de Janeiro, in which the prevalence of flu episodes increases significantly in early winter (June). This aspect was considered to establish the ideal period for the administration of test solutions. Having these aspects in mind, and since one of our aims was quantify the prophylactic effect of homeopathic medicines, we chose April (month that anticipates the beginning of winter there), to provide the children with the tested solutions. During April 2009, all recruited children received these solutions following our protocol, and when the temperatures began to decrease, featuring the arrival of winter (beginning of June), the use of all solutions was interrupted.

This parallel clinical trial was a randomized, triple-blind, placebo-controlled study comprising two phases. It was conducted in the period of April 2009 to March 2010, with 600 children (1–5 years) from the Brazilian Public Health System in Petrópolis (BPHSP), Rio de Janeiro.

The inclusion criteria were: male or female patients, with no apparent disease. Children who lived in geographical areas that were difficult to monitor and those with the following characteristics were excluded: history of wheezing and asthma, HIV infection, immunodeficiency, type I diabetes, malignancies, corticosteroid treatment, congenital anomalies, liver disease, history of at least 1 episode of respiratory infection in the thirty days prior to the beginning of the study. The children who attended the eligibility criteria were consequently invited to take part until there were 600, including only the ones whose guardians signed the written Informed Consent Form. All the procedures were approved by the Ethics Committee at the Federal University of Rio Janeiro, Brazil, under the registration number 194/08. The trial was registered at www.ensaiosclinicos.gov.br and received the Universal Trial Number (UTN: U1111-1169-4297).

The children were randomized followed a numbered list to three intervention groups (Homeopathic Complex, Placebo, and InfluBio), with 200 patients each (1:1:1), block

sizes of 6, using Epi Info software. Following this list, and also to guarantee concealment, independent pharmacists dispensed the test solutions to the health agents who gave the solutions to child's parent or guardian. During the study, neither the families nor the health agents and doctors knew which solution was being given to each child. To this effect, we created a random code of letters (A, B, C) to identify the solutions, which was kept under the custody of the general coordinator of the research.

So, the following groups were blinded: the patients and their guardians; physicians; health agents; and the researchers who performed the data analysis. The physicians (n = 300) and health agents (n = 400) were trained according to an established protocol, which was identical to each child. Besides, an initial assessment performed by these physicians and health agents consisted of data acquisition of anthropometric data, through a standardized questionnaire. Additionally, the children's medical record was consulted, to verify the frequency in which specific symptoms (fever, runny nose, prostration, myalgia, headache and cough) showed up the year before this research.

The "D-day", April 9th (2009), was established to start this project following a protocol previously discussed with physicians and with health agents who belong to BPHSP. Each test solution was administered by the child's tutor twice a day, for 30 days, in April. The dosage applied was 1 drop/year of age, and the sample was previously diluted in a tablespoon of filtered water.

The children were monitored monthly, for 1 year, by the health agents using the same standardized questionnaire, and evaluated the need (or not) of the physician interference. This monitoring followed the criteria of syndromic surveillance for respiratory tract diseases, according to the *International Classification of Primary Care* (ICPC) classification, guided by the Center for Disease Control and Prevention, which considers fever, runny nose, cough, headache, myalgia and prostration, as symptoms of human influenza and acute respiratory infections.²¹ Additionally, all the medical records and entry sheets were revised through the final analysis, aiming to have a high-quality control of data.

Preparation of test solutions

InfluBio was prepared from purified influenza virus sample A/Victoria/3/75 (H3N2), provided by the Virus Surface Structure Laboratory from Paulo de Góes Institute of Microbiology at the Federal University of Rio de Janeiro, Brazil. Briefly, 1 ml of this infectious virus suspension at 10,240 HAU/25 μ L was diluted in 9 ml of sterile distilled water in order to make the first dilution (1:10 dilution), following Brazilian Homeopathic Pharmacopea.¹⁷ This 1:10 sample was submitted to 100 mechanical succussions for 33 s (approximately 3 Hz), using Autic[®] Brazilian machine, originating the first potency, which was named decimal (1 dH, 10^{-1}). This procedure was successively repeated to obtain biotherapy 30 dH (10^{-30}), which was denominated InfluBio.^{17,22}

The other medicine used in this trial was a homeopathic complex composed of bacterial strains (*Streptococcus* and *Staphylococcus*) and inactivated influenza virus, prepared following the same homeopathic procedures¹⁷ until the 30 dH potency, which corresponds to a dilution of 10^{-30} . This medicine is used routinely in patients in the BPHSP, for the prophylaxis and treatment of diseases of the upper respiratory tract.

All test solutions were prepared in the Pharmacy of Roberto Costa's Institute and bottled in amber glasses with a dropper, prepared at the same time and under the same laboratory conditions, under the supervision of a homeopathy pharmacist. The placebo was the biotherapy vehicle, i.e. ethanol 30% (v/v), which is commonly employed as a vehicle for homeopathic medicines.²⁰ All solutions were identical in appearance and taste.

Outcome measures and end points

Primary end points: we compared the number of episodes of flu and acute respiratory infection in one year (2009–2010), as well as the duration, in days, of flu and acute respiratory infection symptoms among the intervention group (InfluBio), the active control (Homeopathic Complex), and Placebo group. To characterize the number of flu and acute respiratory infection episodes, at least two of the following symptoms had to be present: fever (Temperature $> 37.8^{\circ}\text{C}$), runny nose, prostration, myalgia, headache and cough.

Adverse event monitoring: adverse events were reported by child's tutor to the health agents, through an open questionnaire, without a checklist, in order to avoid bias.

Statistical analysis

Analyses per protocol, at 5% level of significance, were carried out in a blind manner using the Statistical Package for the Social Science (SPSS v.17).²³ Using boxplot graphics, the distribution of flu and acute respiratory infec-

tion episodes number was described in a 12-month follow-up. Additionally, Mann–Whitney test was applied to compare the intervention groups.^{24,25,26} To make all pairwise comparisons between groups (placebo *versus* each one of the medicines, and homeopathic medicines among themselves), ANOVA *post-test* (Tukey's honest significance difference) was performed. We also assumed an intention to treat (ITT) analysis, including all missing patient according their original randomization, considering the worst scenario for each individual who presented at least 2 episodes of flu in the follow-up period.

Results

Of the 600 children selected for the study, 445 (74.17%) children finished it and 155 (25.83%) children were classified as dropouts, since they quit during the research period. The main reasons for this loss were change of residence or adherence to private health insurance plans (Figure 1). An important fact to be mentioned is that no child died during the study.

Of the children who participated until the end of the study, the mean age (SD) was 2.4 years without differences among groups (Table 1). The mean body mass index (BMI) was approximately 16 kg/m^2 , the ratio between males and females, in different groups, was similar. When race and area of residence were observed, it was verified that most of the children were classified as white and mulattos living in the urban area. It was observed that, in the previous year, most children had had at least one episode of either flu or acute respiratory infection (Table 1).

In general, the number of flu and acute respiratory infections episodes detected was low. However, the incidence in the group, which received placebo was higher (Figure 2), when compared to the groups which received homeopathic medications, as well as the children who had more than two episodes of flu and acute respiratory infections in the first

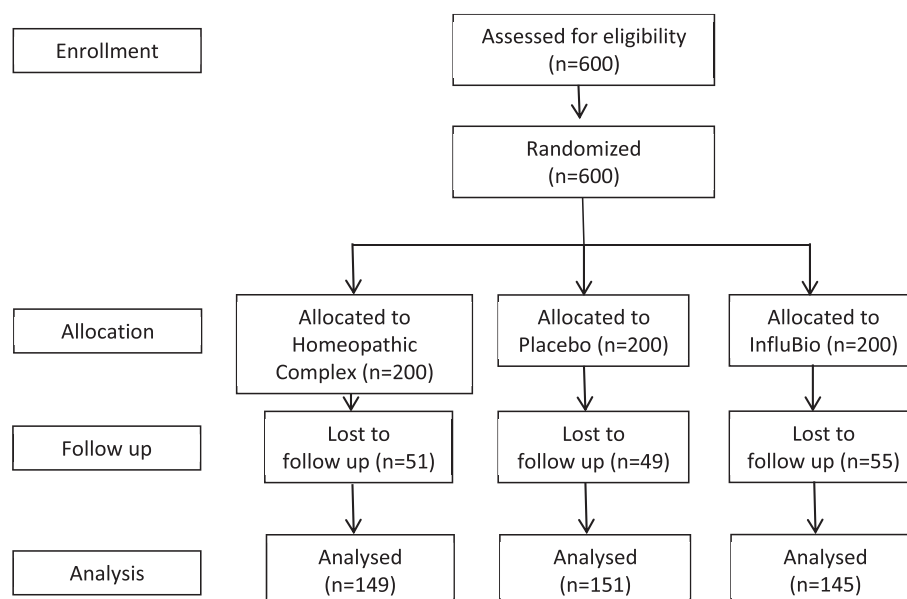


Figure 1 Flowchart of children included in the study.

Table 1 Baseline and socio-demographic characteristics of children enrolled in clinical trial by intervention groups

Characteristics	Homeopathic Complex (n = 149)	Placebo (n = 151)	InfluBio (n = 145)
Age (years)	2.4 ± 1.2	2.4 ± 1.1	2.6 ± 1.1
BMI (kg/m ²)	16.3 ± 2.4	16.3 ± 2.6	16.2 ± 1.6
Sex (n; %)			
Female	63 (42.3)	73 (48.3)	62 (42.8)
Male	84 (56.4)	74 (49.0)	83 (57.2)
Missing	2 (1.3)	4 (2.6)	0
Race (n; %)			
Yellow	1 (7)	0	0
White	77 (51.7)	74 (49.0)	76 (52.4)
Black	18 (12.1)	21 (13.9)	15 (10.3)
Mixed race	38 (25.5)	40 (26.5)	42 (29.0)
Missing	15 (10.1)	16 (10.6)	12 (8.3)
Area of residence (n; %)			
Rural	9 (6)	6 (4)	12 (8.3)
Urban	116 (77.9)	121 (80.1)	113 (77.9)
Rural/Urban	12 (8.1)	12 (7.9)	10 (6.9)
Missing	12 (8.1)	12 (7.9)	10 (6.9)
Previous flu and acute respiratory infection symptomatic episodes* (n; %)			
0	11 (8.9)	16 (12.8)	20 (16.4)
1	43 (35)	47 (37.6)	47 (38.5)
2	28 (22.8)	24 (20.8)	24 (19.7)
3	21 (17.1)	17 (13.6)	12 (9.8)
≥ 4	20 (16.3)	19 (15.2)	19 (15.6)

* Number of flu/ARI episodes detected considering the previous year of this clinical trial (2008).

year after intervention (Table 2). This difference reached statistical significance ($p < 0.001$), when the groups of homeopathic medicine and placebo were compared (Table 3). Nevertheless, no statistically significant difference was detected between the homeopathic medicines ($p = 0.99$), taking into consideration the follow-up period (Table 2; Figure 2). The ANOVA *post-test* (Tukey's HSD) indicated a significantly higher difference when pairwise compari-

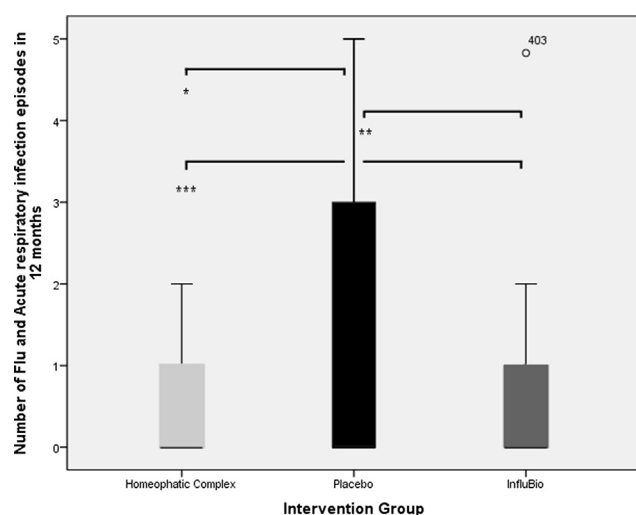


Figure 2 Box-plot of flu and acute respiratory infections episodes number according to intervention groups. * $p < 0.01$: p value comparing Homeopathic Complex *versus* Placebo; ** $p < 0.001$: p value comparing Placebo *versus* InfluBio; *** $p = 0.99$: p value comparing Homeopathic Complex *versus* InfluBio. The outlier point indicates the child that presented more than 4 episodes of flu and acute respiratory infections in 12 months.

sons were done (placebo *versus* each one of the medicines). However, no significance difference was detected when the medicines were compared between themselves, considering the same period (Table 3).

Considering time in months (median, interquartile range) before the appearance of Flu/ARI episodes (Weighted Average), 49 and 52 children who received Homeopathic Complex or InfluBio samples, respectively (May 2009), presented only one flu or ARI episode (Table 2), without any statistically significant difference between these groups ($p > 0.05$). In contrast, children who received placebo showed an increase of flu and acute respiratory infection symptoms in the second month (June 2009; *data not shown*) or in the third month (July 2009).

Additionally, children with flu, acute respiratory infection or other symptoms were always directed to the nearest surgery or received medical care by the coordinator of this research at the Roberto Costa Institute. They were not submitted to laboratory tests, and the symptoms were reported, by guardians, to the health agents. In order to avoid bias in the data collection, the symptoms were registered without a checklist, considering ICPC classification.²¹ It is important to point out that no discomfort or death induced by the use of test solutions were reported by the children's families during the period of this clinical trial.

Discussion

This study was the first to evaluate the prevention and clinical efficacy of two homeopathic medicines, InfluBio and Homeopathic Complex, compared to placebo. A prophylactic effect of the biotherapies tested could be observed since the percentage of children with more than two episodes of flu and acute respiratory infection was lower in patients treated with these homeopathic remedies as compared to those who used placebo.

The present study indicates that the occurrence of respiratory symptoms in children who received placebo was later than in those who received the homeopathic medicines, suggesting a pathogenetic effect triggered by them. Dantas *et al* reported in a systematic review considering 156 homeopathic pathogenetic trials (HPTs), with 2815 volunteers and 143 medicines, the presence of 20,538 pathogenetic effects (median 6.5 per volunteer).²³ HPTs are exclusively applied by homeopathic therapy and based on testing a substance prepared following the homeopathic procedures, with human healthy volunteers, aiming to detect signals and symptoms derived from these homeopathic medicines. In our work, we registered flu and acute respiratory infection symptomatic episodes in the first month after the use of homeopathic medicines; nevertheless, the placebo group only had the same symptoms from the third month on post-intervention. Thus, we can not rule out that the early onset of these symptoms may be due to the pathogenetic effect triggered by the use of homeopathic substances, as detected in other trials.^{23,24}

There are many drugs that are currently prescribed in the treatment of influenza and acute respiratory infection symptoms. Jackson *et al* (2010) did a systematic review

Table 2 Number and percentual values of flu and acute respiratory infections symptomatic episodes in the first year post-intervention

	Number of flu and acute respiratory infections symptomatic episodes in the first year post-intervention (%)				
	0	1	2	3	≥4
Samples Tested					
Homeopathic complex (n = 149)	95 (63.68%)	49(32.9%)	5(3.4%)	0	0
Placebo (n = 151)	102 (67.5%)	1 (0.7%)	2 (1.3%)	27 (17.9%)	19 (12.6%)
InfluBio (n = 145)	90(62.1%)	52 (35.9%)	2 (1.4%)	0	1* (0)

* Outlier child who presented more than 4 episodes of flu and acute respiratory infection symptomatic episodes

to evaluate the prophylactic effect of these drugs, showing positive results; nevertheless, these authors signalized the need for further studies with specific populations, like the elderly and children.⁶ In fact, Shun-Shin verified the existence of a post-exposure prophylaxis when neuraminidase inhibitors were used in pediatric patients.

Our results indicated that participating children were similar in clinical and socio demographic characteristics, suggesting that randomization was successful. Besides, all the children presented a healthy profile, and the number of children who abandoned this study was homogeneous considering the three groups (Table 1).

The literature shows that flu and acute respiratory infections isolated symptoms are very common in childhood. This is an important fact since these patients are subject to excess hospitalizations, medical visits and need for antibiotic use.^{25,26} Additional studies showed that influenza in childhood has a significant economic impact causing school absenteeism, parental absenteeism from work, and secondary illness in families, due to infection transmission.^{27–29}

Petropolis, the city in which this study was carried out, presented cold and wet climatic characteristics, favoring the emergence of flu and acute respiratory infection. Besides these climatic aspects, the children who participated in this study belong to low economic classes and were attended by the public health service, which adds important economic aspects to the present study. Although Brazil does not have a database about influenza infection costs, in Italy, Esposito *et al* (2011) verified that this cost can reach about € 132/day/child.³⁰ This is an important point to be discussed given the economic reality of the families attended by the public health system in Brazil. The homeopathic solutions tested in this work are cheaper when compared to traditional medicines used to treat flu and acute respiratory episodes. This aspect increases the importance of this clinical trial, considering that each 10 ml ho-

meopathic bottle costs nearly € 1.50 and lasts one month for each child patient.

In the year prior to this clinical trial, the Information System of Epidemiological Surveillance Influenza (Sivep_Gripe/Brazil) registered 9.5% of total hospital demand of flu syndrome, with the following rates: children aged 0–4 years (43.3%), followed by the range of 5–14 years (22.9%) and 15–24 years (10.9%). The other age groups were responsible for 22.8% of the cases.³¹ These data reinforce the importance of the present study, considering the high susceptibility of children and the need of new medicines, as homeopathy, with prophylactic potential and absence of side effects.

Safety aspects

The low incidence of adverse events in homeopathy has been demonstrated previously.^{32–34} In the present study, the quantification of adverse effects was done without a checklist not to bias the results. This procedure may have contributed to the absence of these effects reported, considering that, in this case, the patient did not have knowledge of the types of incidents that could appear in the period of research.

It is important to mention that children who used homeopathic medicines sometimes presented symptoms of flu and acute respiratory infection one month after the use, probably related to treatment. This clinical profile is common observed after traditional vaccination, which could be justified by immune system activation. In contrast, children who received placebo presented these symptoms after three months of the beginning of research; i.e., approximately in July, when in Brazil the incidence of flu and acute respiratory infection is high because of the winter. Another key point detected in this study is that the children who received homeopathic medicines presented, in general, only one episode of flu and acute respiratory infection, while the placebo group had three episodes (Table 3). These results showed that both medicines tested were superior to placebo, suggesting their prophylactic effect against flu and acute respiratory infections.

Despite the difficulties, the monitoring of the children was crucial for the recording of the data analyzed. Some other restrictions included the large number of people and professionals involved and the length of this clinical trial. These limitations may have contributed to the dropout of 25.83% (155) of the children studied. These losses, however, were distributed evenly among the groups, showing the efficacy of the randomization procedure.

Table 3 Pairwise comparisons of number of flu and acute respiratory infection symptomatic episodes considering 12 months of follow-up

Intervention Group	Compared to	p value (Tukey's HSD)
Homeopathic Complex (0; 0–1)	Placebo (0; 0–3)	<0.001
InfluBio (0; 0–1)	Placebo (0; 0–3)	<0.001
Homeopathic Complex (0; 0–1)	InfluBio (0; 0–1)	0.99

Our promising results should motivate other controlled clinical studies to quantify the homeoprophylactic potential as an alternative to conventional allopathic medicines to prevent other diseases.

Conclusion

This clinical trial showed that the use of homeopathic medicines prevent flu and acute respiratory infection symptomatic episodes in children, suggesting a homeopathic prophylactic potential. The use of homeopathic medicines to prevent different diseases should be encouraged in the Public Health System, considering that homeopathy is a safe, low-cost and effective therapy.

Conflict of interest

None of the authors have a conflict of interest in the respect to the present work.

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References

- Garigliany MM, Adélite H, Lambrecht B, et al. Influenza A strain-dependent pathogenesis in fatal H1N1 and H5N1 subtype infections of mice. *Emerg Infect Dis* 2010; **16**(4): 595–603.
- WHO – World Health Organization. *Influenza: Overview*, <http://www.who.int/topics/influenza/en/>; 2012.
- Jacobs B, Young NL, Dick PT, et al. Canadian Acute Respiratory Illness and Flu Scale (CARIFS): development of a valid measure for childhood respiratory infections. *J Clin Epidemiol* 2000; **53**: 793–799.
- Barata RCB, Waldman EA, de Moraes JC, et al. Gastroenteritis and acute respiratory infections among children up to 5 years old in area of Southeastern Brazil, 1986-1987.I – Acute respiratory infections. *Rev Saude Publica* 1996; **30**(6): 553–563.
- Kuiken T, Taubenberger J. Pathology of human influenza revisited. *Vaccine* 2008; **26**(4): D29–D66.
- Jackson RJ, Cooper KL, Tappenden P, et al. Oseltamivir, zanamivir and amantadina in the prevention of influenza: a systematic review. *J Infect* 2011; **62**: 14–25.
- Shu-Shin M, Thompson M, Heneghan C, et al. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomized controlled trials. *BMJ* 2009; **339**: b3172.
- Peters PH, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc* 2001; **49**(8): 1025–1031.
- Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 2001; **285**(6): 748–754.
- Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999; **341**(18): 1336–1343.
- Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. *Lancet* 2000; **355**: 827–835.
- Jefferson T, Doshi P. Multisystem failure: the story of anti-influenza drugs. *BMJ* 2014; **348**: g2263 <http://dx.doi.org/10.1136/bmj.g2263>.
- Couceiro JNSS, da Silva PM, dos Santos MGM, et al. Natural piperine as a new alternative against influenza viruses. *Virus Res* 2005; **10**: 27–32.
- Arias CF, Escalera-Zamudio M, Soto-Del Río MD, et al. Molecular anatomy of 2009 influenza virus A (H1N1). *Arch Med Res* 2009; **40**: 643–654.
- Gong J, Fang H, Minyong L, et al. Potential targets and their relevant inhibitors in anti-influenza fields. *Curr Med Chem* 2009; **16**: 3716–3739.
- Michaelis M, Doerr HW, Cinati JJ. Novel swine-origin influenza A virus in humans: another pandemic knocking at the door. *Med Microbiol Immunol* 2009; **198**: 175–183.
- Brasil. *Ministério da Saúde, Farmacopéia Homeopática Brasileira*. 3rd edn; 2011.
- Costa RA. *Nosódios Vivos*. 1st edn. Rio de Janeiro: Farmácia Homeopática Átomo Ltda., 2002.
- Siqueira CM, Costa B, Amorim AM, et al. H3N2 Homeopathic Influenza Virus Solution Modifies Cellular and Biochemical Aspects of MDCK and J774G8 Cell Lines. *Homeopathy* 2013; **102**: 31–40.
- Ministério da Saúde Brasil. *Política Nacional de Medicina Natural e Práticas Complementares – PMNPC*. Brasília, DF: Fev de. Available from: <http://bvsms.saude.gov.br/bvs/publicacoes/ResumoExecutivoMedNatPratComp11402052.pdf>; 2005.
- www.cdc.gov/EID/content/14/6/917-Techapp.pdf.
- Fontes AL. *Farmacía Homeopática: Teoria e Prática*. 2nd edn. São Paulo: Manole, 2005.
- Dantas F, Fisher P, Walach H, et al. A systematic review of the quality of homeopathic pathogenetic trials published from 1945 to 1995. *Homeopathy* 2007; **96**: 4–16.
- Dominici G, Bellavite P, di Stanislao C, et al. Double-blind, placebo-controlled homeopathic pathogenetic trials: Symptom collection and analysis. *Homeopathy* 2006; **95**: 123–130.
- Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; **342**: 232–239.
- Neuzil KM, Mellen BG, Wright PF, et al. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; **342**: 225–231.
- Hurwitz ES, Haber M, Chang A, et al. Studies of the 1996–97 inactivated influenza vaccine among children attending day care. *J Infect Dis* 2000; **182**: 1218–1221.
- Neuzil KM, Hohlbein C, Zhu Y. Illness among schoolchildren during influenza season. Effect on school absenteeism, parental absenteeism from work, and secondary illness in families. *Arch Pediatr Adolesc Med* 2002; **156**: 986–991.
- Esposito S, Principi N. Different influenza vaccine formulations and adjuvants for childhood influenza Vaccination. *Vaccine* 2011; **29**: 7535–7541.
- Esposito S, Cantarutti L, Molteni CG, et al. Clinical manifestations and socio-economic impact of influenza among healthy children in the community. *J Infect* 2011; **62**: 379–387.
- http://portal.saude.gov.br/portal/arquivos/pdf/gve_7ed_web_atual_influenza.pdf.
- Rossi E, Endrizzi C, Panozzo MA, et al. Homeopathy in the public health system: a seven-year observational study at Lucca Hospital (Italy). *Homeopathy* 2009; **98**: 142–148.
- Shafei HF, AbdelDayem SM, Mohamed NH. Individualized homeopathy in a group of Egyptian asthmatic children. *Homeopathy* 2012; **101**: 224–230.
- Nayak C, Singh V, Oberai P, et al. Homeopathy in chronic sinusitis: a prospective multi-centric observational study. *Homeopathy* 2012; **101**: 84–91.