



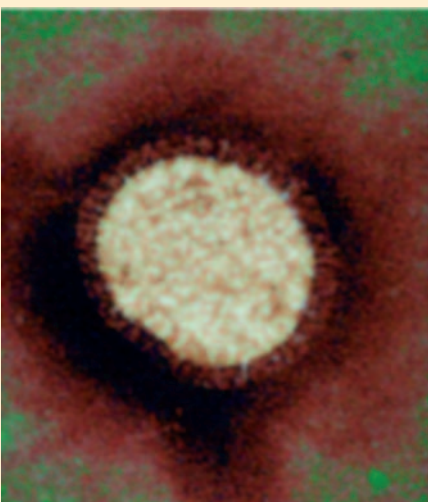
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SUMMARY

Between October 2004 and February 2005, 100 school children aged 2- 6 years, following free choice pediatric care in 4 pediatric consulting clinics operating within the National Health Service (ASL 2 - Milan) underwent a random preventive therapy with flu vaccine (no.45), *Guna*[®]-*Flu* (no.45), or both (no.10). The number of untreated children in the control group was 76. The trial highlights the non inferiority of the homeopathic *Guna*[®]-*Flu* treatment vs the reference conventional therapy having an important role against influenza and parainfluenza infections that can be explained by the immunoprophylactic activity of the homeopathic medicine even in cases of frequent antigenic drifts peculiar to the influenza virus.

The data concerning the synergistic effect deriving from flu vaccine + *Guna*[®]-*Flu* are particularly interesting. Moreover, both immunoprophylactic protocols show a considerable reduction in antibiotic therapy recurrence, absence from school and from work (relatives) and evident case history seriousness in non responders. *Guna*[®]-*Flu* tolerability was total. During this trial only one case of vaccine adverse reaction was registered.

KEY WORDS INFLUENZA, PREVENTION, FLU VACCINE, *GUNA*[®]-*FLU*, ANTIGENIC DRIFT, ANTIGENIC SHIFT



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COMPARATIVE EVALUATION OF *GUNA*[®]-*FLU* vs VACCINE FOR THE PREVENTION OF INFLUENZA SYNDROME IN PEDIATRICS

– A PROSPECTIVE, MULTICENTRIC, RANDOMIZED, CONTROLLED CLINICAL TRIAL

INTRODUCTION

Influenza is an epidemic disease, its etiological agent belongs to the viral family *Orthomyxoviridae*.

The influenza viruses are classified from the serological aspect into **types A, B and C** according to the antigenicity of the core proteins.

Type A viruses, in turn, are subdivided into **subtypes** according to the *hemagglutinin (HA)* and *neuraminidase (NA)* surface antigens.

In aquatic birds, the main *reservoir* of the influenza virus, 15 HA and 9 NA subtypes of influenza virus type A have been found: only 3 of these (H1N1, H2N2, H3N2) are associated with human disease.

The influenza virus, like all RNA viruses, is characterized by great antigenic variability, which is manifested especially in type A:

Antigenic shift is defined as a particularly frequent type of genotypic rearrangement, in which one or more segments of the viral genome are replaced

by the corresponding segment(s) of the influenza viruses of the avian infection reservoir (pigs are also a reservoir of influenza virus); this usually happens in the case of a pandemic, as in 1957 and 1968.

Antigenic drift is a type of slighter antigenic variation, which usually manifests in inter-pandemic periods within a single subtype; it consists of the replacement of a limited number of amino acid residues in the antigenic sites of the HA.

It should be borne in mind that the variants of the influenza virus can produce epidemics when the HA has been modified in such a way that the virus can avoid being neutralized by a sufficient number of people. In this case, the antigenic variations must occur in at least **2 antigenic sites** of the HA molecule.

TAB. 1

INFLUENZAL SYNDROME
<p>Definition: Acute respiratory disease caused by infection by influenza viruses: the disease involves the upper and/or lower respiratory tract; it is often accompanied by systemic signs and symptoms such as <i>fever, headache, myalgia and lack of energy.</i></p>
RRI (RECURRENT RESPIRATORY INFECTIONS)
<p>Definition: Infections of the upper and lower respiratory tract occurring with a frequency greater than 1 episode per month in the period of maximum exposure (November-April).</p>

EPIDEMIOLOGY

The influenza virus infects a variable percentage of the world's population each year (on average hundreds of millions of persons). An epidemic is defined as an infection of ~ 15-20% of the population and a pandemic occurs when 50% of the world's population is affected within the space of 1-2 years.

- In Western countries, **25%** of children aged less than 1 year and **18%** of children aged between 1 and 4 years are affected by influenza or para-influenza infections characterized by **inflammation of the upper or lower respiratory tract, tonsillitis, otitis, or enteritis.**

These infections are relevant for epidemiological and economic reasons (because of the healthcare expenditure involved) and for social reasons (because

of the days lost from school or taken off work by the parents).

DEFINITION, ETIOLOGY, COMPLICATIONS, DIAGNOSTIC COURSE

Influenza is an acute respiratory disease characterized by an incubation period of 48-72 hours, involving the upper and/or lower respiratory tract and often accompanied by systemic signs and symptoms such as fever, headache, myalgia and lack of energy (TAB. 1).

In adult patients, the viral titres in rhinopharyngeal washings usually fall to minimal levels from the 5th day. Consequently, adults can transmit the infection for 4-5 days.

Children aged < 6 years are known to be more sensitive to viral attack because of their **immune system immaturity.** This involves more frequent contraction of influenza or influenza-like illness and lasts longer compared to the adult patient who is characterized by a mature immune system. Immune immaturity is dependent on 3 factors:

- Immune virginity
- Functional immaturity of the immune system
- Immunodepressant action produced by viral infections.

Greater sensitivity to infection is increased by any early admission of the child to a child community (day nursery, kindergarten) where the virus can spread via an airborne route. A child's exposure to passive smoke (especially by smokers in the family environment) can favor the development of respiratory tract infections, as can environmental pollution, especially in urban and industrial areas. According to WHO instructions, the influenzal syndrome is diagnosed when the following conditions are met:

- **Sudden rise in temperature (> 39°C)**
- **Onset of muscle and joint pains**
- **Respiratory symptoms (pharyngolaryngodynia, rhinorrhoea, cough, dyspnoea) associated with inflammatory phenomena that develop in the course of the infection: pharyngotonsillitis, rhinitis, tracheitis, bronchitis (the latter more frequent in children up to 5 years of age).**

The most common **complications** of influenza are otitis media, bacterial sinusitis and secondary bacterial pneumonia caused in most cases by *Staphylococcus aureus, Streptococcus spp, Haemophilus influenzae.*

- The fundamental diagnostic phase for the presence of suspected influenzal syndromes consists of the recent medical history and general physical examination.

TAB. 2

SUBDIVISION OF THE PATIENTS
<ul style="list-style-type: none"> ● Group A: Anti-influenza vaccine (n=45) ● Group B: Guna®-Flu (n=45) ● Group C: Guna®-Flu+ anti-influenza vaccine (n=10) ● Group D: No treatment – control (n=76)

TAB. 3

First page **A** and last page **B** of the Mother's diary, which includes 7 items relating to 8 conditions (rhinitis, otitis, tonsillitis, pharyngitis, tracheitis, bronchitis, bronchopneumonia, enteritis) and 2 symptoms (vomiting, headache), assessment of the treatment and any adverse reactions.

A **A MOTHER'S DIARY**

CHILD'S FIRST AND LAST NAME:
DATE OF BIRTH:
TELEPHONE NUMBER:

RHINITIS:

1	Date of start of episode								
2	Days of fever								
3	Maximum temperature								
4	Days of absence from school								
5	Days of absence from work								
6	Antibiotic therapy (yes/no)								
7	Other therapy								

OTITIS:

	Date of start of episode								
	Days of fever								
	Maximum temperature								
	Days of absence from school								
	Days of absence from work								
	Antibiotic therapy (yes/no)								
	Other therapy								

B

Compliance (child)

a. Guna®-Flu: Poor

Adequate

Optimal

b. Anti-influenza vaccine: Poor

Adequate

Optimal

Adverse reactions

a. Guna®-Flu: yes no

If yes, what:

b. Anti-influenza vaccine: yes no

If yes, what:

THE STUDY

This clinical study centered upon preventive treatment of influenza and influenza-like symptoms with the **anti-influenza vaccine, Guna®-Flu** or **both**.

Having considered the aspects concerning the genetic lability of the influenza virus described above:

- The vaccine stimulates a **response of the antibody type** possessing specificity and memory. This involves minor preventive efficacy in the presence of antigenic *shift* or *drift*.
- Guna®-Flu evokes a **response of the cell-mediated type (cytotoxic T lymphocytes and Natural Killer cells)** primarily, producing specific and non-specific cytolysis of the infected cells, thus bypassing the problem of the antigenic variability of the influenza virus.

The data published in the international literature are in line with our thesis.

The vaccines have an average efficacy of 68% (with confidence intervals between 49% and 79%).

This is due to the specific action against

the two influenza viruses A and B.

In adults, the average effectiveness of the vaccines for the outcome "influenzal syndrome" is much lower (~ 12% with a confidence interval between 6% and 18%) since their preventive action is tempered by the concomitant presence of numerous other pathogenic agents that cause the influenza syndrome.

Vaccination does not protect against influenza viruses of a different strain from that of the vaccine or against other viruses that cause respiratory diseases with symptoms similar to those of influenza. There are over 200 antigenically distinct viruses responsible for **influenza-like illnesses** (ILI): Rhinovirus, Coronavirus, Respiratory Syncytial Virus, Meta-Pneumovirus, Para-Influenza Virus, Adenovirus.

Virologists and infectiologists themselves recognise that one of the limits of inactivated anti-influenza vaccines employed is represented by the incomplete stimulation of the immune system, in particular, of mucosal and cellular immunity.

Although the percentage of secondary undesirable effects after inoculation of

the anti-influenza vaccine is very low, the following phenomena are observed:

- **Local:** skin reactions of brief duration (max. 48 h) such as erythema, swelling, tenderness.
- **Systemic:** (possible in individuals who have not been in contact previously with the influenza virus) such as fever, headache, myalgia, chills, all symptoms of the influenza type, which can occur in attenuated form 6-8 h after vaccination and last up to 48 h.

STUDY AIMS

The present clinical study had 4 main aims:

- To demonstrate the efficacy of homeopathic treatment in the prevention of the influenza syndrome in the pediatric age group.
- To demonstrate the non-inferiority of homeopathic treatment compared to conventional treatment.
- To demonstrate the lesser use of antibiotic therapy in the group treated with the homeopathic medicine or

TAB. 4

ODDS RATIO (OR)
<p>Definition:</p> <p>Odds Ratio is a measure of association.</p> <ul style="list-style-type: none"> ● If it is > 1, it indicates a positive association with the disease (poor protection from the disease in question). ● If it is < 1, it indicates a negative association with the disease (protection from the disease in question).

TAB. 5

CONFIDENCE INTERVAL (CI)
<p>Definition:</p> <p>The confidence interval expresses the margin of statistical likelihood of the data.</p> <ul style="list-style-type: none"> - CI 95% means that the data can be expected in 95%, and are very highly significant.

with the vaccine compared to the untreated control group.

- To demonstrate the absence of adverse reactions to the homoeopathic treatment.

For this purpose, a **prospective, multi-centric, randomized, controlled study** was prepared in a population of **176 children** under the care of a general paediatrician in 4 pediatric clinics operating within the National Health Service (ASL 2 in Milan).

The period of the study was from October 2004 to February 2005.

RATIONALE OF THE STUDY

The rationale of the study and its

comparison of preventive measures such as the **anti-influenza vaccine** and a **homoeopathic immunostimulant** is based upon the consideration that the influenza virus is characterised by high **antigenic variability**, which is manifested as frequent *shift* or *drift*, which renders the antibody response induced by the vaccine partially ineffective.

PATIENTS AND METHODS

■ INCLUSION

Children who experienced at least 4 influenzal episodes or RRI (recurrent respiratory infections) in the year preceding the study and in the same pe-

riod of observation (October-February).
 - At time zero of the study, all the included children were in good health.

■ INCLUSION CRITERIA

176 children attending the 4 participating paediatric clinics who met the following requirements were included in the study:

- Aged between **2 and 6 years**
- **Attending school**
- Inclusion also of **allergic individuals**.

■ EXCLUSION CRITERIA

Excluded were children

- with major immunodepression
- with ongoing immunosuppressant treatment.

■ SUBDIVISION OF PATIENTS

(TAB. 2)

- Group A** (n = 45): treatment with anti-influenza vaccine
- Group B** (n = 45): treatment with Guna®-Flu
- Group C** (n = 10): treatment with Guna®-Flu + anti-influenza vaccine
- Group D** (n = 76): no treatment (control group).

■ THERAPEUTIC PROTOCOLS

- ▶ **Group A: VAXIGRIP® Bambini Split** (antigens A/New Caledonia/20/99 (H1N1)-IVR-116; A/Moscow 10/99 (H3N2) A/Panama 2007/99 (RESVIR 17); B/HongKong/330/2001/B/Shangdong 7/97).

The vaccine complies with WHO recommendations for the northern hemisphere and with the EU guidelines for the 2002-2005 seasons.

- children 6-35 months: 1st dose: 0.25 ml - to be repeated after 4 weeks at the same dosage (if first vaccination)
 - children over 35 months: 1st dose: 0.5 ml - to be repeated after 4 weeks at the same dosage (if first vaccination).
- Route of administration: i.m. or deep s.c. injection.

TAB. 6

OR = Odds Ratio
 CI = Confidence Interval

MORBIDITY			
	OR	(95% CI)	
Anti-influenza vaccine group (A)	0,22	0,10	0,45
Guna®-Flu group (B)	0,38	0,16	0,89
Guna®-Flu + anti-influenza vaccine group (C)	0,11	0,04	0,33

▶ **Group B:** Guna®-Flu children 6-35 months: 1/2 monodose per week for 8 consecutive weeks; - children over 35 months: 1 monodose per week for 8 consecutive weeks. Route of administration: sublingual.

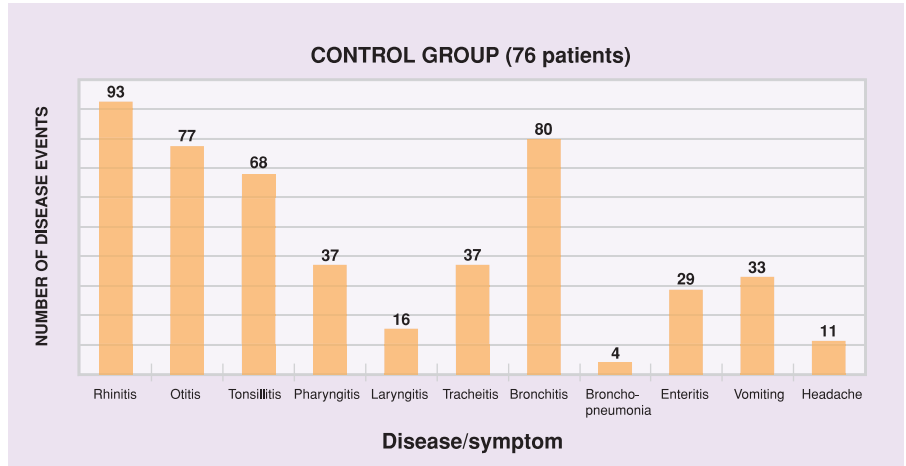
▶ **Group C:** GUNA®-FLU + ANTI-INFLUENZA VACCINE.

▶ **Group D:** no treatment (CONTROL).

FOLLOW UP

During the observation period, data were collected on the possible development of: rhinitis, otitis, tonsillitis, pharyngitis, tracheitis, bronchitis, bronchopneumonia, enteritis, vomiting, headache; for each of these conditions, the data **indicating efficacy** were recorded in the mother's diary (TAB. 3):

- Number of days of fever
- Maximum temperature recorded
- Number of days absent from school
- Number of days absent from work of a parent
- Use of antibiotic therapy.



TAB. 7

Untreated control group. Number of events per single disease considered.

Because of the characteristics of this group, it is not possible to calculate the OR or CI.

GUNA®-FLU

Guna®-Flu is a complex homoeopathic medicine composed of Aconitum napellus 5C, Belladonna 5C, Echinacea 3C, Vincetoxicum 5C, Anas barbariae hepatis et cordis extractum 200CK, Cuprum 3C, Influenzinum 9C, saccharose q.s. 1 g. In Guna®-Flu there are 2 distinct remedy actions:

- 1) Remedies for immunostimulation
- 2) Remedies for control of symptoms.

1) Remedies for immunostimulation

Effective remedies for immunostimulation are: **Anas barbariae 200CK**, **Influenzinum 9C**, **Vincetoxicum officinale 5C**.

- Anas barbariae 200CK

This is obtained from an autolysate of duck liver and heart.

Influenza viruses find a reservoir in the heart and liver of this bird species, a healthy carrier of the influenza viruses in inter-epidemic periods.

The homoeopathic preparation of these tissues that are vehicles of specific antigens causes them to be fully assimilable to the nosode (indirect nosodotherapy).

- Influenzinum 9C

This is the nosode of influenza.

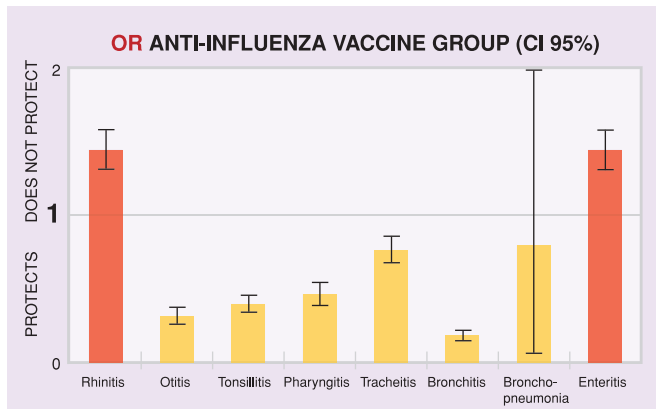
The rationale for its use in Guna®-Flu follows the rule of current etiological resemblance. Its action mechanism is assimilable to that of active homoeopathic seroprophylaxis, which makes it useful in treatment as well as prevention.

- Vincetoxicum officinale 5C

Induction of non-specific immunostimulation through an increase in macrophages, T-lymphocytes and polymorphonuclear cells.

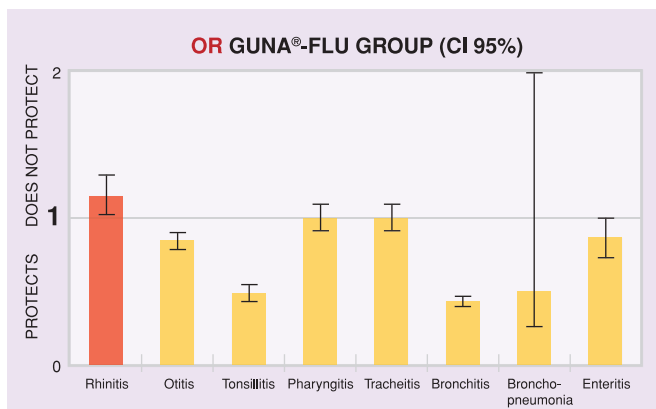
TAB. 8

- Diseases recorded in the group treated with anti-influenza vaccine.
OR = Odds Ratio
CI = confidence interval



TAB. 9

- Diseases recorded in the group treated with Guna®-Flu.
OR = Odds Ratio
CI = confidence interval



In the nucleus of remedies for immunostimulation it is possible to identify **2 sub-nuclei** (FIG. 1):

- The first, formed by *Anas barbariae* and *Influenzinum*, works by stimulating **specific cell-mediated** immunity: T-helper lymphocytes and cytotoxic T-lymphocytes (the latter produce specific cell lysis in cells infected by the influenza virus) and non-specific cell-mediated immunity: NK (*Natural Killer*) cells.
- The second, consisting of *Vincetoxicum officinale*, works by stimulating **non-specific humoral immunity** (network of cytokines, γ -interferon and lysozyme in particular).

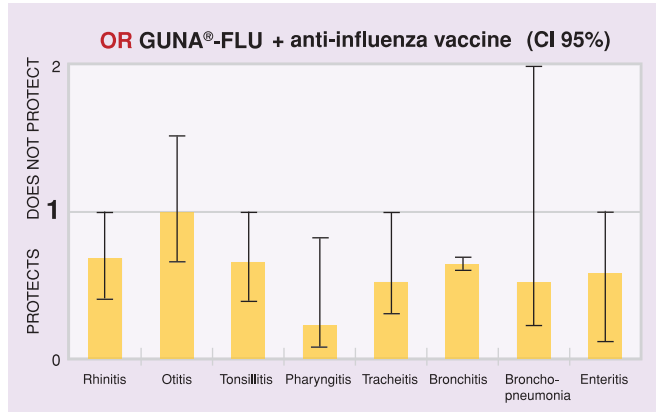
Synergy of action is assumed for *Anas barbariae* and *Influenzinum* and **complementarity** for these with *Vincetoxicum*.

- The higher dilutions for the remedies of this nucleus are expressed in *Anas barbariae* and *Influenzinum* as pathogenic viral strains - obviously made non-pathogenic by the homeopathic preparation - and the lower one in *Vincetoxicum*, as vegetable of very low toxicity.

USE OF ANTIBIOTICS			
	OR	CI 95%	
Anti-influenza vaccine group (A)	0,53	0,49	0,58
Guna®-Flu group (B)	0,56	0,52	0,60

TAB. 10

- Use of antibiotics in the 2 groups compared (A, B). OR = Odds Ratio CI = confidence interval



TAB. 11

- Diseases recorded in the group treated with Guna®-Flu + anti-influenza vaccine. OR = Odds Ratio CI = confidence interval

2) Remedies for control of symptoms (FIG. 2)

The remedies that work in this direction are: **Aconitum 5C, Belladonna 5C, Echinacea angustifolia 3C and Cuprum 3C.**

These homeopathic remedies are indicated in the initial phases of the inflammatory process (neurogenic and vascular phase) and in the acute febrile episode in particular.

This means that Guna®-Flu is indicated also in the **treatment** of influenzal and para-influenzal symptoms and **not only** in the prevention of the influenza syndrome and colds.

The presence of these remedies also has a precise rationale from the point of view of synergy with the remedies of the nucleus of immunostimulation.

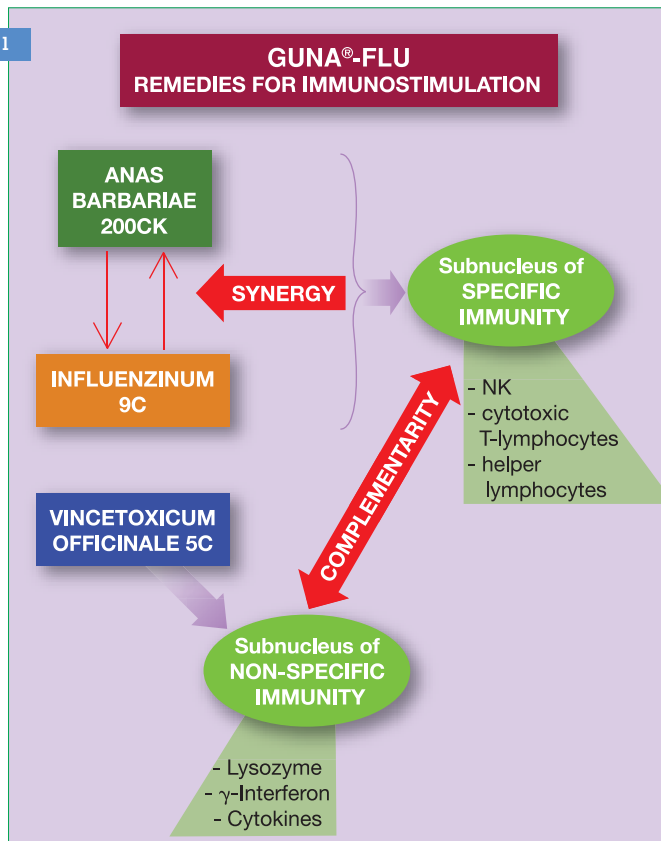
STATISTICAL ANALYSIS AND RESULTS

Results were drawn up and analysed according to the **Odds Ratio** model of analysis (TAB. 4), taking into account the **Confidence Interval** (TAB. 5).

This model of statistical analysis allows assessment of the **non-inferiority** of Guna®-Flu vs. anti-influenza vaccine in the prevention of the influenza syndrome and colds since the result expresses the significance of positivity or negativity of preventive efficacy absolutely and not as a percentage scale of efficacy (TAB. 6).

FIG. 1

Guna®-Flu. - Remedies for immunostimulation.



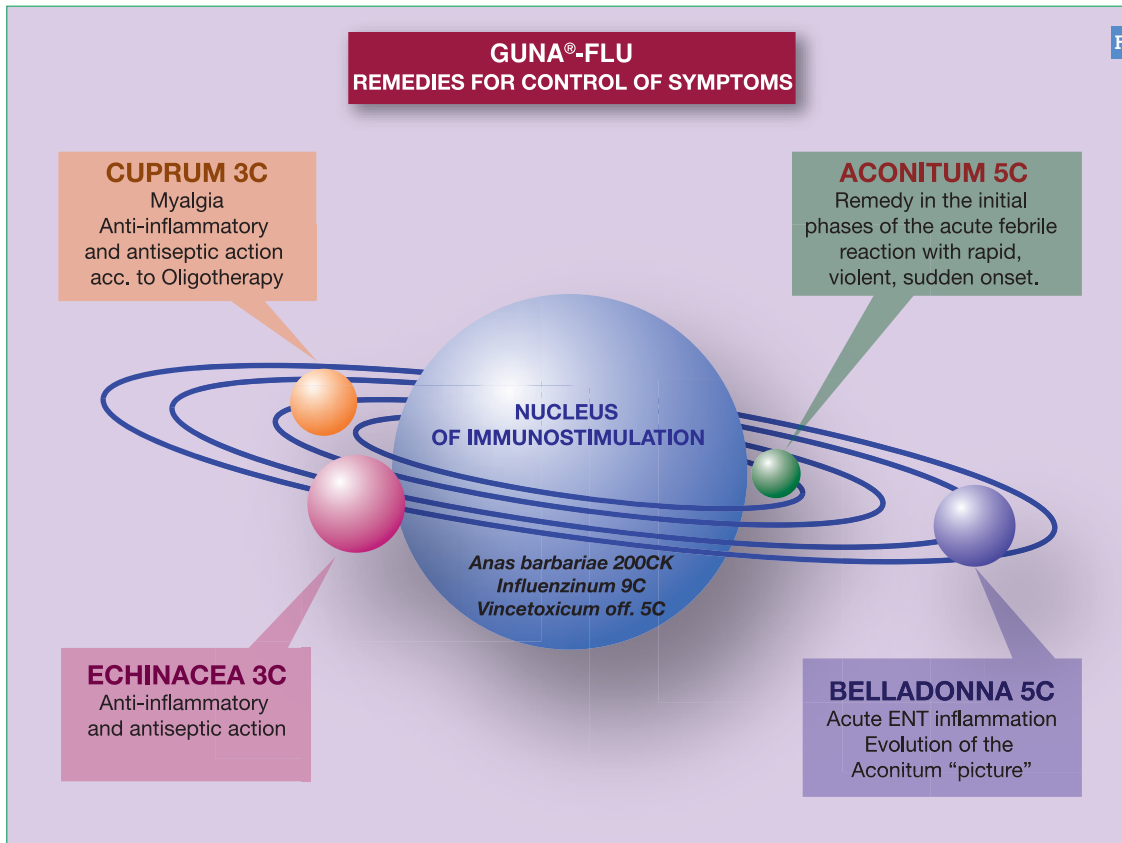


FIG. 2

Guna®-Flu.
– Remedies for control of symptoms

DISCUSSION

In this study, both protective measures considered showed **clear preventive efficacy** in the treated children compared to the control group (TAB. 7).

In particular, each protective measure showed greater preventive affinity for some clinical pictures of the influenzal syndrome (TAB. 8, 9).

The percentage of episodes of acute respiratory infections treated with antibiotics was reduced drastically from 65% to 40% in the treated groups (TAB. 10).

No side effect was recorded in the children included in the Guna®-Flu group. The compliance of children and their parents with the homeopathic medicine was optimal.

A point for reflection for any future trials of Guna®-Flu vs. anti-influenza vaccine is the fact that there is a **possibility of therapeutic overlap between the two medicines**, which is plausible in relation to their mechanism of action: antibody immunostimulation possessed of specificity, memory and very high selectivity for the vaccine but "defenseless" toward

viral drift; cell-mediated immunostimulation capable of providing effective cover by Guna®-Flu even in the case of viral drift (TAB. 11). ■

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