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# Prevention of Influenza Episodes With Colostrum Compared With Vaccination in Healthy and High-Risk Cardiovascular Subjects: The Epidemiologic Study in San Valentino

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The efficacy of a 2-month treatment with oral colostrum in the prevention of flu episodes compared with anti-influenza vaccination was evaluated. Groups included healthy subjects without prophylaxis and those receiving both vaccination and colostrum. After 3 months of follow-up, the number of days with flu was 3 times higher in the non-colostrum subjects. The colostrum group had 13 episodes versus 14 in the colostrum + vaccination group, 41 in the group without prophylaxis, and 57 in nontreated

subjects. Part 2 of the study had a similar protocol with 65 very high-risk cardiovascular subjects, all of whom had prophylaxis. The incidence of complications and hospital admission was higher in the group that received only a vaccination compared with the colostrum groups. Colostrum, both in healthy subjects and high-risk cardiovascular patients, is at least 3 times more effective than vaccination to prevent flu and is very cost-effective.

**Key Words:** influenza prevention—colostrum—vaccination

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Influenza (flu) causes many deaths and a large amount of costs worldwide. Vaccines standardized to contain hemoagglutinin protein of different viruses and antiviral drugs are available for its prophylaxis or treatment. These products are aimed mainly at the prevention of serious consequences, including hospitalization and death, that affect particularly the weaker members of the population such as children, individuals aged 65 years and older, and patients debilitated with chronic disease. Even though the recommendations for prevention

of influenza are well defined,<sup>1,2</sup> a significant number of influenza-associated hospitalization occur among the elderly<sup>3</sup> and in children.<sup>3,4</sup>

The occurrence of new “drift”<sup>5</sup> or a new emerging virus<sup>6</sup> may reduce the cost-effective performance of vaccines and antiviral drugs, however, and the impact of vaccination benefit sometimes is considered to be overestimated.<sup>7,8</sup> New prevention tools should be available that may improve the defense against the virus that causes flu. One of these could be colostrum.

Colostrum is produced by the mammary gland within 48 to 73 hours after the birth of offspring. This period is so significant to ensure a correct immunologic status that without colostrum, many newborn mammals do not survive. Human colostrum is an important source of proteins, fats, carbohydrates, and vitamins and minerals, and includes several biologically active molecules essential for immunity,

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such as immunoglobulins (Ig) and growth factors. For several reasons, however, human colostrum is not easily available, storable, or usable as a supplement. Bovine colostrum is the most common source as food supplement. Despite the lack of a defined composition profile and fluctuation of Ig titer, all types of bovine colostrum contain neutralizing Ig against pathogens.<sup>9</sup>

Factors present both in bovine and human colostrum, even though not identical are comparable, and most elements are present in higher quantities and concentrations in bovine colostrum. In general, the specific antibodies found in colostrum include those for *Escherichia coli*, *Salmonella* spp, *Streptococcus* spp, *Helicobacter pylori*, *Candida* spp, rotavirus, and other common pathogens.<sup>10</sup> Some clinical studies have already shown that colostrum includes factors that are able to reduce chronic diarrhea in immunodeficient subjects,<sup>11,12</sup> diarrhea caused by rotavirus in children,<sup>13</sup> and improve symptoms of upper respiratory tract infections in adults.<sup>14</sup>

The aim of this study was the evaluation of the use of oral colostrum in preventing flu episodes linked to winter compared with anti-flu vaccination, and also the consideration of a comparable group subjects using no prophylaxis. The colostrum used was derived from nonimmunized animals and characterized by a standardized composition, and results obtained in this study cannot necessarily be produced by all types of colostrum. Also, a high-risk group with cardiovascular problems was included because an episode of flu in these subjects can easily become severe and severely increase morbidity and even mortality.

## METHODS AND MATERIALS

### Study Design

Subjects analyzed in this study were evaluated within the framework of the epidemiologic screening project (PAP/PEA) in San Valentino, Vasto, and Spoltore (Abruzzo, Italy), which repeats—with different characteristics, being based on high-resolution ultrasound imaging of the arterial wall—the framework of the Framingham Study. The PAP/PEA study, in its 12th year of activity, includes constant contact with the subjects in the local populations that are being evaluated, which is ideal for this type of monitoring study. The study was performed as a clinical registry trial.

### Patients

#### Inclusion Criteria

In Part 1 of the study, 144 healthy individuals of both sexes (age range, 30 to 80 years) were included and divided in 4 groups. Two similar groups were formed by subjects who underwent flu vaccination within 2 weeks before the inclusion: one group of 44 subjects took colostrum, and the other group of 39 did not take any type of immunostimulant or antiviral drug. A third comparable group of 38 subjects received only colostrum, without a flu vaccination. The prophylaxis groups were compared with a fourth group of 23 subjects who did not use any prophylaxis.

#### Exclusion Criteria

Excluded were subjects with severe clinical disease, chronic diseases, an infection not controlled by treatment, and those with diabetes. Patients who had hospital admissions or surgery within 4 months before inclusion, for any reason, were also excluded.

### Treatment

Subjects in the colostrum groups used oral tablets (one daily, at 8:00 AM, for 8 weeks). The composition of the colostrum, in chewable tablets (AR<sub>D</sub> Colostrum, Corcon srl, Milan, Italy) containing 400 mg of defatted bovine freeze-dried colostrum with its characteristics, is reported in Table 1. The use of other drugs, and particularly anti-infective drugs and antibiotics, were avoided.

Vaccination had been performed within 2 weeks before inclusion into the follow-up period. The type of vaccine administered was the standard anti-flu vaccine supplied by the Italian National Health Service.

Evaluation of the outcome was made considering as targets:

- a. the presence and frequency of flu episodes within the 2 months of prophylaxis;
- b. the presence and frequency of flu episodes in the third month (without prophylaxis);
- c. the total number of days of malaise and/or lost working days;
- d. the relative costs due to the loss of working days;
- e. the need for treatments and hospital admissions; and
- f. the number of event-free subjects.

**TABLE 1.** Composition of the Freeze-Dried Colostrum Used in the Trial

Product	Quantity/g	Product	Quantity/g
<b>Vitamins</b>		<b>Amino acids</b>	
Vitamin A	4-5 µg	Alanine	40-45 µg
Vitamin B <sub>1</sub>	1-1.5 µg	Arginine	35-40 µg
Vitamin B <sub>2</sub>	1-1.5 µg	Aspartic acid	15-20 µg
Vitamin B <sub>6</sub>	0.25-0.5 µg	β-alanine	1-2.5 µg
Vitamin B <sub>12</sub>	0.5-1 ng	β-aminoisobutyric acid	6-8 µg
Vitamin B <sub>9</sub>	0.15-0.2 µg	Citrulline	6-8 µg
Vitamin C	2.5-5 µg	Cystine	1-2 µg
Vitamin D <sub>3</sub>	5-11 ng	Glutamine	40-50 µg
Vitamin E	3-5 µg	Glutamic acid	200-270 µg
Ubiquinone Q10	0.1-0.2 µg	Glycine	30-35 µg
<b>Minerals</b>		Histidine	7.5-12.5 µg
Sodium	8.5 mg	Isoleucine	30-35 µg
Potassium	126 mg	Leucine	60-85 µg
Calcium	2.7 mg	Lysine	50-65 µg
Magnesium	1.0 mg	Methionine	6-9 µg
Iron	0.0015 mg	Ornithine	3-5.5 µg
Copper	0.00035 mg	Phenylalanine	32.5-33 µg
Zinc	0.0003 mg	Phosphoethanolamine	150-225 µg
Chromium	0.0001 mg	Phosphoserine	50-75 µg
Selenium	0.00002 mg	Proline	35-60 µg
Phosphoric acid	3 mg	Serine	25-40 µg
<b>Immunoglobulins</b>		Taurine	0.6-0.12 mg
IgG	200-350 mg	Threonine	17.5-27.5 µg
IgA	15-35 mg	Tryptophane	40-60 µg
IgM	5-10 mg	Tyrosine	17.5-27.5 µg
		Valine	60-80 µg
		<b>Growth factors (GF)</b>	
		Insulin-like GF 1	1-1.5 µg

After the admission visit, all subjects were reevaluated by phone or personal contact every 2 weeks with a questionnaire.

Part 2 of the study included very high-risk subjects, including end-stage coronary patients and patients with pulmonary hypertension or severe cardiovascular problems. The protocol was comparable to the one described in healthy individuals (part 1). However, because of the higher risk, all groups had prophylaxis (there was no control group without prophylaxis).

### Statistical Analysis

Results were evaluated according to the analysis of variance (flu episodes and days of malaise), and a comparison (Mann-Whitney) non-parametric test was performed at the end of the study. An intention-to-treat analysis (ITTA) was performed considering the difference between the numbers of negative events (flu episodes plus the number of dropouts) in the different groups.

## RESULTS

### Part 1

All groups were comparable (Table 2) for age and sex distribution. Dropouts were determined by nonmedical causes, including failure to come to the control evaluation, failure to follow prescriptions or minor errors, and breaking of the prophylaxis protocol.

### Episodes and Days of Flu or Malaise

In the colostrum group (Table 3), the average number of flu episodes in 2 months was 0.335 (range, 0 to 3) and was significantly lower than the average in the vaccination group and in controls. In the colostrum group there was 25% of days of disease considering the total in the nonprophylaxis group ( $P < .05$ ). The days of disease in the colostrum group were 30% of those recorded in the vaccination group ( $P < .05$ ). The difference is clinically relevant and significant, even considering

**TABLE 2.** Details of the Healthy Evaluation Groups (Part 1)<sup>a</sup>

Study Details	No Prophylaxis	Vax + Col	Col	Vax	Total
F/M	13:10	22:19	20:17	22:14	77:60
Included	23	44	39	38	144
Completed <sup>b</sup>	23 (55 ± 8)	41 (54 ± 7)	37 (53 ± 6)	36 (54 ± 8)	137
Dropouts	0	3	2	2	7

Vax = vaccination; Col = colostrum; F/M = female/male.

a. Initially 144 subjects were included, 137 completed the 3-month follow-up, and 7 dropouts were determined by nonmedical causes.

b. The mean ages and SD are shown in parenthesis.

**TABLE 3.** Evaluation of Parameters Modified by Prophylaxis in the Four Groups<sup>a</sup>

	No Prophylaxis	Vax + Col	Col	Vax
Number	23	41	37	36
a. Flu episodes ≤2 months	1.3 (0-4)	0.34 (0-2)	0.33 (0-3)	1.1 (0-5)
b. Flu episodes in 3 months	1.8 (0-4.3)	0.35 (0-3)	0.34 (0-3)	1.6 (0-4)
c. Days of disease in 3 months	13.2 (1-29)	4.3 (0-13)	4.6 (0-14)	11.3 (3-31)
d. Costs <sup>b</sup> (Euros)	1384	412	404	1124
e. Admissions (total/group)	2	—	—	1
f. Event-free subjects	5	17	19	10
Total episodes (3 months)	41	14	13	57
ITTA <sup>c</sup>				
Event subjects + dropouts	18 + 0	24 + 3	18 + 2	26 + 2
Total	18	27	20	28
Total/inclusion number	18/23 (0.78)	27/41 (0.65)	20/37 (0.54)	27/36 (0.78)

a. Data are shown as mean values and ranges, corresponding to days of malaise.

b. Vaccination plus treatment plus lost days.

c. Intention-to-treat analysis (ITTA): the total number of event subjects (patients having at least one flu episode) is added to dropouts (total). This number is divided by the included subjects, and dropouts are therefore considered as events. Events in the vaccination and control groups were 1.44 times higher than in the colostrum group. The difference is statistically significant ( $P < .05$ ).

the total of 3 months of observation ( $P < .05$ ) including 1 month without colostrum.

The total number of days of disease was 3 times larger in untreated controls and in subjects who had been treated with vaccination. The group treated with vaccination and colostrum had results strictly comparable with the results observed in the group receiving only colostrum.

The relative costs were significantly lower in the 2 colostrum groups ( $P < .05$ ) than in the others groups and were comparable in the 2 colostrum groups.

The total number of episodes (days of malaise) in the colostrum group was 13 versus 14 in the colostrum + vaccination group: 41 in the group without prophylaxis and 57 in the vaccination group, which is significantly higher ( $P < .05$ ) than in the 2 colostrum groups. The higher number of episodes may suggest that vaccination itself may induce a number of days with malaise in some individuals.

The difference in the incidence of events associated with flu, plus the dropouts in each group, between colostrum subjects and controls was 4.2 (178/41.4); the incidence of events in nontreated controls was therefore 4.2 times higher ( $P < .05$ ). The difference in incidence in events between colostrum subjects and vaccination subjects was 3.9 (163.8/41.4); therefore, the incidence in events in vaccination subjects was 3.9 times higher than the incidence in the colostrum subjects ( $P < .05$ ).

### **Intention-to-Treat Analysis**

The total number of event subjects (patients having at least 1 flu episode) is added to dropouts (total). This number is divided by the included subjects. The dropouts are therefore considered as events. Events in the vaccination and control groups were 1.44 times higher than in the colostrum group. The difference is statistically significant ( $P < .05$ ).

**TABLE 4.** Details of High-Risk Study Subjects (Part 2)<sup>a</sup>

	Vax + Col	Col	Vax	Total
F/M	15:6	14:6	11:8	40:20
Included	22	21	22	65
Completed <sup>b</sup>	21 (67 ± 7)	20 (68 ± 6)	19 (68 ± 7)	60
Dropouts	1	1	3	5
Events	3	3	6 <sup>c</sup>	12
ITTA (%)	4/22 (18)	4/21 (19)	9/22 (40.9) <sup>c</sup>	17/65 (26)
Hospital admissions	1	2	5 <sup>b</sup>	8

ITTA = intention-to-treat analysis.

a. Part 2 of study included very high-risk subjects (end-stage coronary patients, patients with pulmonary hypertension or severe cardiovascular problems). The protocol was comparable to the one described in healthy individuals (part 1). However due to the higher risk all groups had prophylaxis (there was no control group without prophylaxis).

b. Data in parenthesis are the mean ages ± SD.

c.  $P < .05$ .

## Part 2

The second part of the study (Table 4) included very-high-risk subjects (end-stage coronary patients, patients with pulmonary hypertension or severe cardiovascular problems). Of a group of 65, 60 completed the study: 21 were treated with colostrum, 20 with vaccination in association with colostrum, and 19 with vaccination only. The prophylaxis groups were clinically comparable for age and sex distribution.

## Events

As summarized in Table 4, only 3 of 20 patients completing the study in the colostrum group had flu associated with an important bronchopulmonary complication. In the vaccination + colostrum group, 3 of the 20 patients completing the study also had cardiopulmonary problems. Finally, in the vaccination group, 6 of 19 patients completing the study had severe flu with cardiopulmonary complications that resulted in 1 death. Hospital admissions in these groups are also summarized in Table 4. The incidence of complications and hospital admission (ITTA) was significantly higher ( $P < .05$ ) in the group using only vaccination.

## Costs

Costs evaluated during the study, mainly owing to the lost working days, were parallel to the occurrence of events. In the colostrum group, costs were very close to 30% of those observed in the noncolostrum groups.

If we consider hospital admissions (not observed in the colostrum group, in part 1 of the study), particularly bronchopulmonary complications that followed the flu episodes in elderly patients, the difference in costs becomes even higher considering that some of

these episodes lasted well beyond the 3 months of observation. No hospital admission was recorded in the colostrum group and this observation, which should be verified by larger studies, is of particular interest.

## Tolerability

No significant problems with tolerability or side effects were observed during the study. Compliance was very good (>88%), as only 12% of the tablets were not used or not correctly used. This finding is very useful considering that it is a prophylaxis and not a disease, which usually attains a higher level of compliance.

## DISCUSSION

Vaccinations have generally produced a striking improvement in public health, reducing mortality and morbidity through an improvement in specific immunity, by increasing awareness, and very often, just by a generic stimulation of immunity. However, variation in virulence, antigenic characteristics, and in protein content of several viruses, reflecting their adaptation to changing situations, make the results of flu vaccination quite unpredictable.

Several objections to the routine use of vaccination have been raised. Many subjects seem to have a limited benefit from vaccination, which is active in developing immunity, particularly in young subjects because their immune response is very effective. In elderly subjects, the immune response seems to be very limited, and therefore, vaccination in these subjects seems to have a minor effect and benefit.<sup>15</sup> There is also the problem of

the type of virus used for prevention, which may be different from the one that actually causes disease in specific areas, populations, and times.<sup>6,16,17</sup> The use of vaccination in subjects with severe immunologic and inflammatory disorders<sup>18</sup> can be also questioned because most vaccines may not be safe, including those individuals with rheumatoid arthritis; concerns have also been raised about flu vaccination in pregnancy.<sup>19</sup>

The efficacy of flu vaccination and its cost-effectiveness is probably questionable because of the possible presence of unknown and known side effects.<sup>20,21</sup> A relation between the incidence of intussusception associated with the first dose of vaccine in infants was recently shown.<sup>22</sup> It is theoretically possible that long-term effects may result from elements present in the vaccination material that are presently unknown, such as unknown viral fractions. Even though flu vaccination has the lowest incidence of side effects compared with other types of vaccination,<sup>20</sup> complications may occur at a variable distance in time from the vaccination; therefore, it is difficult to define and evaluate them carefully.

The use of colostrum, on the contrary, is practically free of side effects. Furthermore, the dosage used in this study is very low, corresponding to 400 mg of colostrum.

Chronic diarrhea in HIV infection,<sup>11,12</sup> diarrhea caused by rotavirus infection in children,<sup>13</sup> and upper respiratory infection in adults,<sup>14</sup> have been treated successfully with a high concentration of purified immunoglobulins from colostrum, which is necessary once an infection has already taken place. For prophylaxis, however, a lower concentration of a multicomponent large-spectrum product such as colostrum can be sufficient.

A very low concentration of insulin-like growth factor I,<sup>23</sup> lactoferrin, and lactoperoxidase<sup>24</sup> can be sufficient to determine protection as a nonspecific defense, and similarly, complement factors<sup>25</sup> and oligosaccharides<sup>26,27</sup> can increase the body's capability to produce passive immunity. A low concentration of colostrum has been found to increase the oxidative burst of leukocytes,<sup>28</sup> and also low concentrations of transforming growth factor- $\beta$ 1, such as that present in colostrum, were able to reduce the gastric damage induced by indomethacin.<sup>29,30</sup>

Colostrums containing different quantities of immunoglobulins were found similarly active in the reduction of endotoxin burden in rats and the infiltration of bacteria in mesenteric lymph nodes.<sup>31</sup> Cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, tumor

necrosis factor- $\alpha$ , and interferon- $\gamma$ , which are present in colostrum,<sup>32</sup> may stimulate production of neutralizing antibodies against hemagglutinin and neuramidase of the virus surface. All these observations indicate that colostrum activity belongs to a combination of protective factors that may allow an antiviral prophylaxis.

In many instances, flu starts from the intestinal tract, and protection *in situ* may be one of the advantages given by colostrum. Local activity in the gut may be the most important factor. However, rotavirus antibody were shown to survive during the passage through the gut, which may also determine systemic immunity.<sup>33</sup>

Very-high-risk subjects, including end-stage coronary patients, patients with pulmonary hypertension, and those with severe cardiovascular problems, usually have a very severe prognosis in case of flu, which almost always is associated with severe bronchopulmonary complications that often lead to hospital admission. The prevention in these patients is very important, but the effects of vaccination in these individuals seem to be of very low efficacy owing to the very reduced immune response.<sup>7</sup> We conclude from our observations that colostrum appears to offer a more effective protection.

A larger study is now in progress. It could indicate that in severely ill subjects with potentially fatal risks from cardiovascular complications, colostrum may offer an important increase in resistance, whereas vaccination, considering both age and the relative decrease in immunologic resistance and activity of these subjects, may be really ineffective or only marginally useful. The efficacy of colostrum in these subjects may be even more important because they may have more complex and severe cardiorespiratory complications. A larger study could provide new data on the efficacy of colostrum as a preventive measure to limit the diffusion and effects of flu in high-risk cardiovascular patients.

## CONCLUSION

The present study suggests a safe and cost-effective method—which still needs more evaluation in specific groups, particularly high-risk cardiovascular patients—that may be considered at least an important clinical alternative to vaccination. There is evidence that in some situations in which vaccination is contraindicated, the use of colostrum may be not only more effective but the only practical solution.

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