

## SCIENCE REPORT

### Summary of Human Clinical Trials on EpiCor<sup>®</sup>

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**Summary:** *Seven human clinical trials conducted with EpiCor show its beneficial immune modulating effects.*

- ❖ *The first two trials studied EpiCor's effect on supporting immune health to reduce potential cold and flu symptoms. Conducted January through March, 2007, one trial was on subjects vaccinated against flu while the other studied subjects who had not been vaccinated. Both trials showed a reduction in total days of sickness in the subjects taking EpiCor.*
- ❖ *A third trial shows EpiCor increased secretory Immunoglobulin A (sIgA) (an integral part of the body's first line of defense).*
- ❖ *The fourth trial examined how EpiCor balances the immune system by increasing sIgA while simultaneously reducing the increase of serum immunoglobulin E associated with allergens. This balancing effect appears to be related to reduced allergy symptoms in trial participants taking EpiCor.*
- ❖ *The fifth trial demonstrated that at least some of the responses to EpiCor can be measured in a very short time frame (2 hours).*
- ❖ *The sixth trial demonstrated that EpiCor can significantly reduce allergy symptoms during periods of high pollen count – especially nasal congestion – while at the same time increasing the body's defense against pathogens as measured by increased secretory IgA.*
- ❖ *The final trial (still ongoing) demonstrates the benefits of EpiCor on exercise induced inflammation*

The results from clinical trials for EpiCor demonstrate its capability to help maintain immune balance. The gold standard for research is the double-blinded placebo-controlled human clinical trial, and six have been completed with EpiCor. Moreover, all the trials described below have either been published, have been submitted for publication, or are in various stages of preparation for submission to peer-reviewed journals. Independent contract research organizations designed and conducted five of the seven trials using appropriate and accepted methodology and statistics. One trial was carried out in-house, again using accepted methods, and another by a well recognized University.

## STUDY OF EpiCor DURING COLD AND FLU SEASON

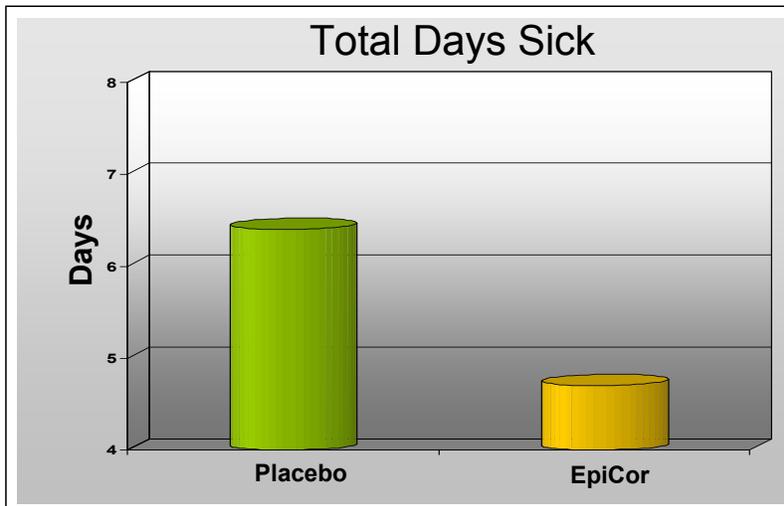
Upper respiratory tract infections are reported to be the most commonly contracted illnesses. Maintaining a balanced, healthy immune system is expected to reduce the likelihood of sick days lost to upper respiratory tract infections (URTI). To determine the effect of EpiCor on maintaining immune balance, two large, independently conducted double-blind placebo-controlled trials were conducted during the 2007 cold and flu season in the Midwest.

In the first trial, the clinical benefits of EpiCor were assessed in a group of over 100 adults who had been vaccinated against flu. The object was to study the effects of EpiCor on incidence and duration of symptoms from upper respiratory tract infections (URTIs). This large group was chosen to represent the general vaccinated population.

The trial took place in South Dakota during the expected worst cold and flu months – January, February, and March. Subjects received physical examinations at screening to ensure a healthy study population, and were assigned randomly to receive either EpiCor (500 mg) or placebo. Fasting blood samples were taken at randomization, week 6, and at week 12 (when the trial ended). In addition, each subject was instructed to record the incidence, duration and severity of cold and flu symptoms.

In the subjects taking EpiCor, the incidence of URTI symptoms was statistically significantly reduced. A statistic known as the “p-value” was  $<0.05$  – meaning that the reduction in URTI symptoms in the EpiCor was statistically significant. Additionally, in the cases when the EpiCor subjects did get URTIs, the duration of the symptoms was significantly shorter. The total number of days sick was reduced by 26%.

**Figure 1. The Effect of EpiCor on the Number of Days of Sickness Experienced by Vaccinated Subjects**



The second trial was carried out using the same methodology, in the same time frame, on a group of 110 people who had not been vaccinated against flu. Again there was a reduction in the incidence and duration of URTIs, and the total number of days sick was reduced by 26%.

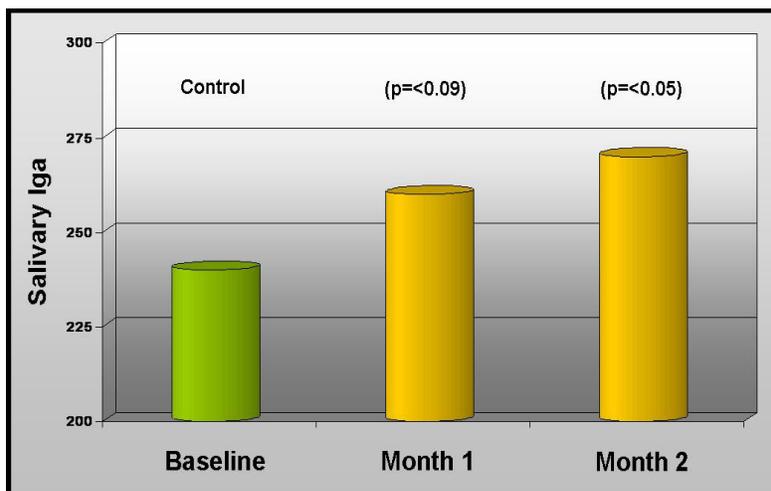
## STUDY OF EpiCor EFFECT ON sIgA

Secretory immunoglobulin A (sIgA) is an antibody that is part of the human body's first line of defense and integral to a healthy immune system. This antibody is produced from the gut-associated lymphoid tissue, which comprises over 70% of the total immune system. As the majority of human infections arrive via breathing, touching and eating, sIgA is an essential part of the body's initial immune defense against pathogen exposure. Accordingly, Embria sponsored a human clinical trial to establish whether EpiCor provides immune support by causing increased beneficial salivary sIgA levels.

Twenty-two people were recruited who had never taken EpiCor. Before subjects consumed any EpiCor in this open-label in-house trial, baseline concentrations were established for sIgA by measuring saliva samples, which were collected twice a day, three times a week, for one month. The subjects were then given one 500 mg capsule of EpiCor per day for 60 more days while researchers continued monitoring sIgA levels.

After 30 days, results showed a strong trend for increased sIgA over baseline, and after 60 days the average sIgA levels among the subjects were significantly higher than the baseline levels (Figure 2). These results indicate EpiCor increased this important immune defense component in just a matter of a few weeks. It also suggests that it takes time for the body to obtain the full benefits from EpiCor, and that continuous use is needed for the most beneficial effects.

**Figure 2. The Effect of EpiCor® on Salivary Secretory IgA**

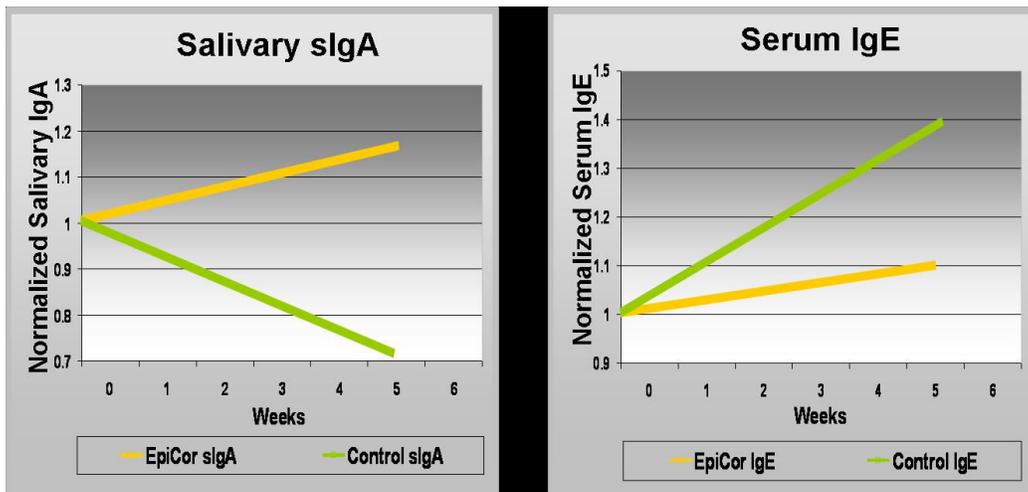


## STUDY OF BALANCING EFFECT OF EpiCor ON sIgA AND SERUM IgE

Immune balance requires the immune system to respond appropriately to stressors that affect overall health. Another human clinical trial investigated the effects of EpiCor on several important markers of distinct immune functions. In this double-blind placebo-controlled trial, subjects were given either EpiCor (500 mg) or placebo for five weeks. At the end of five weeks, the salivary sIgA increased while serum IgE decreased. Though not reaching full statistical significance due to both the small number of subjects and the shortness of the trial, this was a strong trend and is hence very encouraging.

These results help confirm the results of other trials demonstrating the efficacy of EpiCor. At the same time, the observation of decreased serum IgE in the EpiCor group suggests the important immune balancing effects of EpiCor. Specifically, since this trial was conducted in the spring when allergies are a problem for many people, serum IgE was expected to show an unfavorable increase because this immune parameter is associated with the onset of allergies. In fact, such an increase in IgE was seen in the results from the subjects receiving the placebo. The EpiCor group, however, had IgE levels remain nearly at baseline, giving laboratory confirmation of the subjects' reporting fewer allergy problems than usual (Figure 4). Moreover, this benefit of EpiCor consumption is reflected in the standardized questionnaire showing significantly fewer health complaints from the EpiCor group.

**Figure 3. The Effect of EpiCor® on Salivary IgA and Serum IgE**

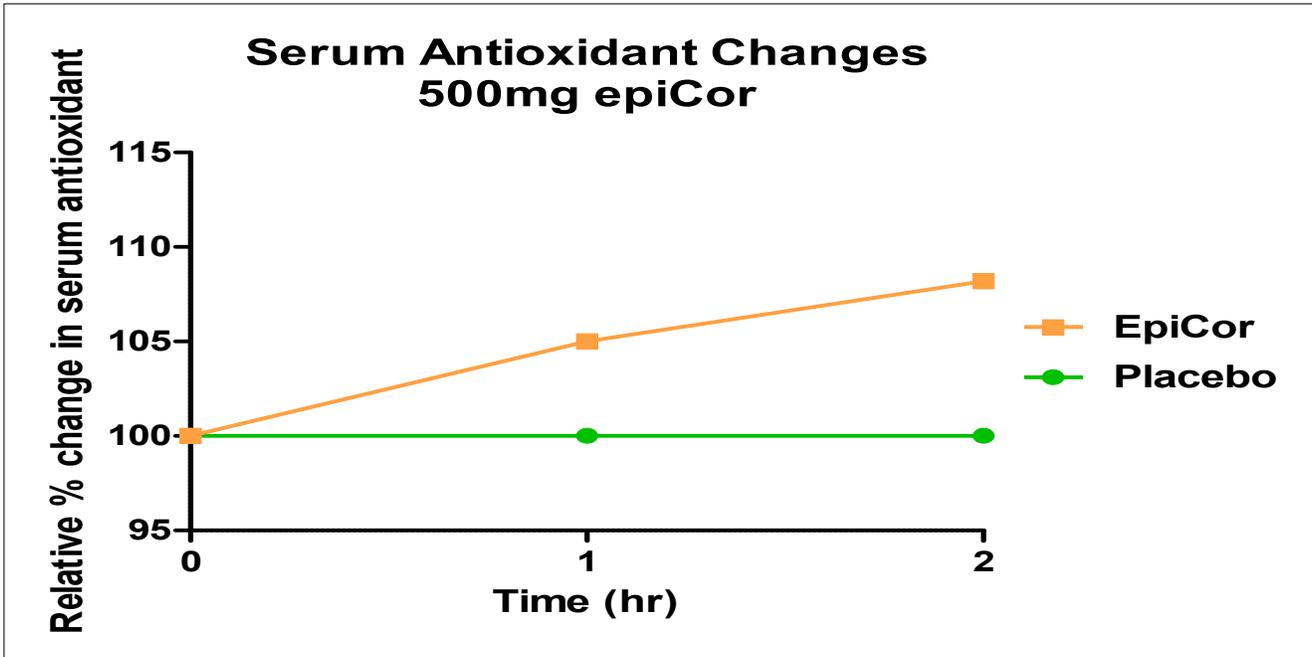


It was also observed in this trial that cytokine profiles were shifting in the EpiCor group – from T-helper 1 (Th1) (pro-inflammatory) to T-helper 2 (Th2) (pro-adaptive) and vice versa – again demonstrating the immune balancing properties of EpiCor. This result is consistent with EpiCor research using animal models that also demonstrated the multiple effects of EpiCor and its ability to help balance the immune system and prevent over-reaction in any direction.

## RAPID IMMUNE RESPONSES TO EpiCor CONSUMPTION IN HUMANS

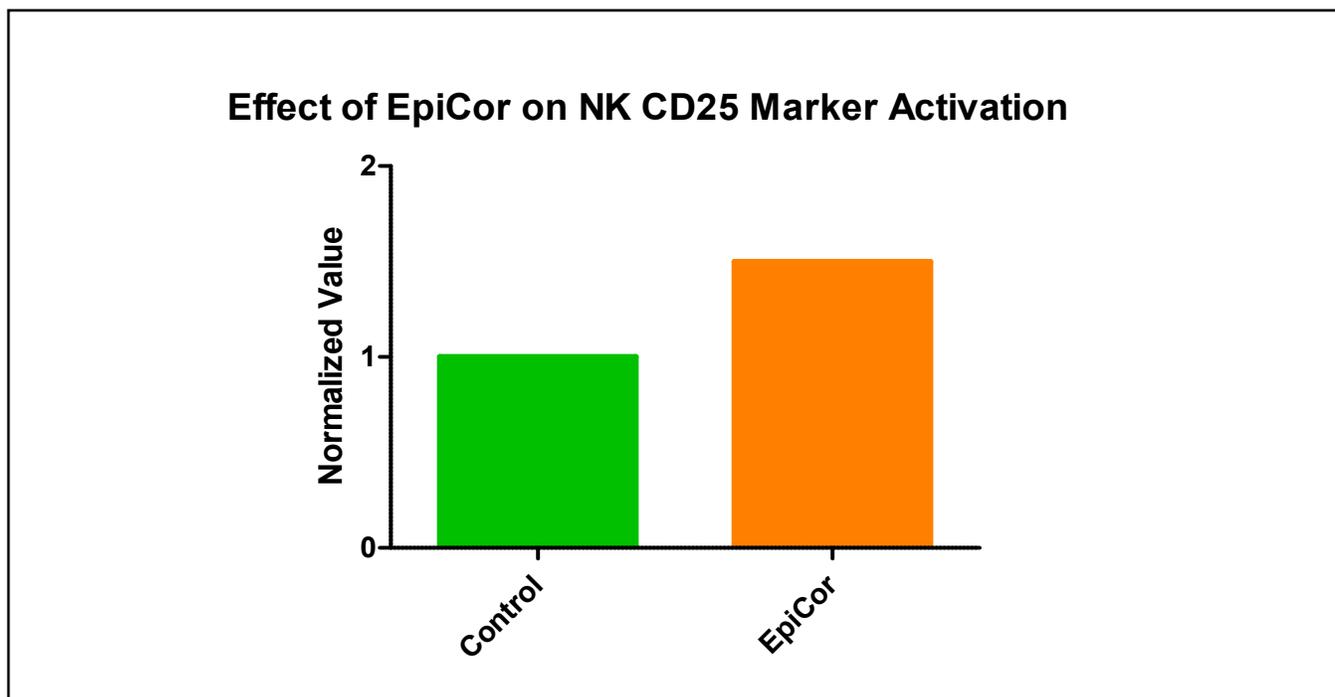
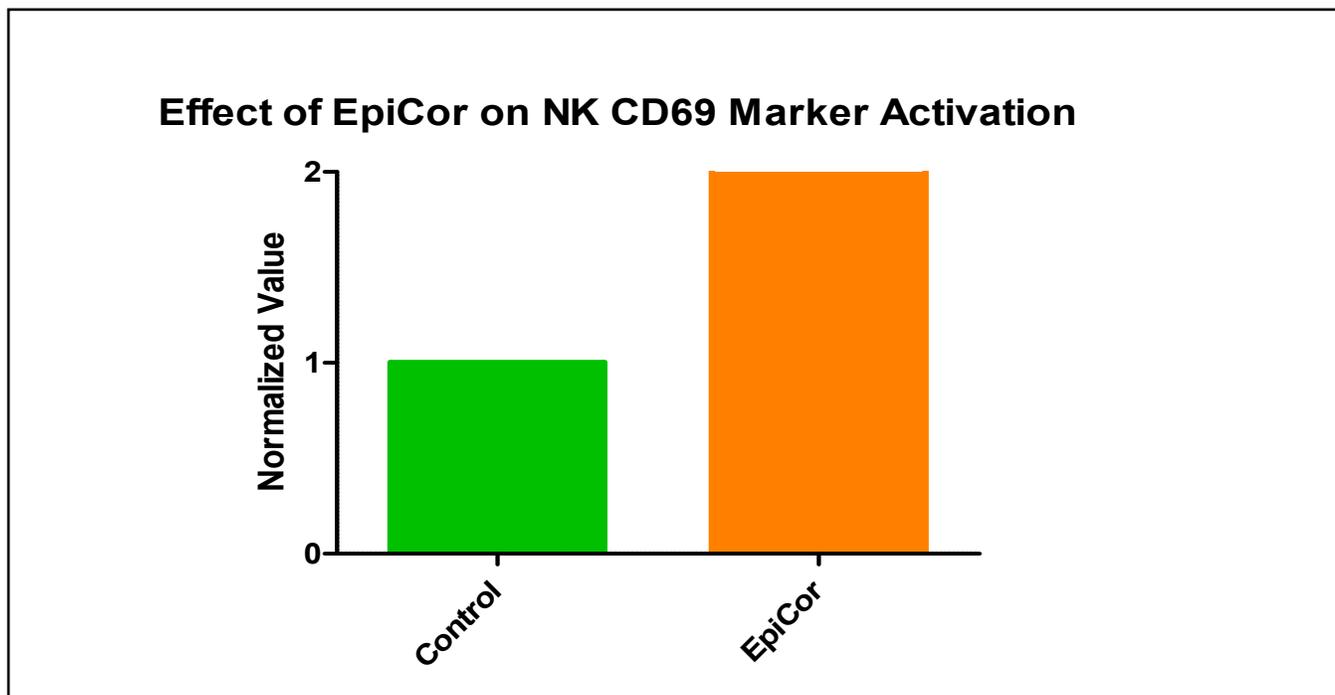
A human clinical carried out with 500 mg of EpiCor clearly demonstrated that the antioxidant levels in serum start rising very rapidly. After 2 hours the EpiCor group had statistically significantly higher antioxidant levels than the placebo group.

Figure 4. The Effect of EpiCor® on serum antioxidant levels



Furthermore, it has been shown that natural Killer Cell activities are stimulated in the same time scale. Figure 6 shows that within one hour of ingesting a recommended daily dose of EpiCor, both the CD25 and CD69 markers of serum NK cells show statistically significant activation.

Figure 5. The Effect of EpiCor® on Natural Killer Cell Activation



These rapid responses complement the slower, modulatory effects of EpiCor, such as the increase in salivary sIgA and the ability to reduce over-reaction to common allergens.

## **RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFECT OF 500 mg ONCE A DAY EpiCor ON ALLERGY SYMPTOMS**

Previously EpiCor demonstrated a significant ability to reduce the risk and duration of cold and flu-like symptoms in two large randomized controlled trials. Since EpiCor also seemed to provide simultaneous immune enhancement and immune balance during these and other studies EpiCor was next tested against common allergens or seasonal allergies in a follow-up clinical trial.

In a clinical trial (conducted in South Dakota during the 2008 spring allergy season), over 80 healthy subjects who tested positive for seasonal allergies were randomized to once a day 500mg EpiCor versus placebo during a 12 week time period during spring and summer when total pollen counts were high. The highest total pollen counts occurred during the first 6 weeks of the clinical trial, and during this high pollen count period, the EpiCor group showed statistically significant reductions in several symptoms commonly associated with seasonal allergies. EpiCor demonstrated the greatest reductions in symptom severity when total pollen counts were highest, as would be expected. The largest symptomatic impact occurred with nasal congestion. The most significant symptom reductions were:

### ***Nasal Symptoms***

- Reduction mean severity ( $p=0.03$ )
- Runny nose ( $p=0.005$ )
- Congestion ( $p=0.04$ )

### ***Eye Symptoms***

- Non significant reduction in itchiness and sneezing

Subjects were also asked to record when they used rescue medication for severe allergies, and those taking EpiCor utilized statistically significantly less rescue medication for allergies compared to placebo during the highest pollen count period of the study. Biochemical data mirrored the effectiveness observed in the allergy diary and questionnaire comparing EpiCor to Placebo:

- The number of selective allergy producing lymphocytes was reduced in the nasal smears ( $p<0.05$ );
- Downward trend of mean eosinophil percentage in nasal smears ( $p=0.056$ )
- Downward trend of mean serum basophil percentage ( $p=0.082$ ).

However, the body's immune system wasn't being depressed, but modulated, as reflected by the fact that subjects taking EpiCor had significantly increased levels of sIgA (showing improved defense against pathogens), with a trend towards reduced IgE.

### **Iowa State University Exercise Trial.**

A two phase, Double Blind Placebo Controlled exercise trial is currently being carried out at ISU (Iowa State University). Phase I looked at the effect of EpiCor on subjects undergoing aerobic exercise- induced inflammation and was considered a preliminary trial. There was a statistically significant decrease in levels of pro-inflammatory markers in the EpiCor group. Phase II (currently ongoing) uses resistance exercise-induced inflammation, and it is anticipated that this will result in greater levels of inflammation.

## **SUMMARY OF EpiCor EFFICACY SHOWN IN HUMAN CLINICAL TRIALS**

The results from these seven clinicals demonstrate the potential for EpiCor to play a beneficial role in helping healthy individuals maintain immune balance. EpiCor has been shown to have a positive effect on key parts of the immune system that perform important functions against challenges. Embria's commitment to science ensures continued responsible research into EpiCor and its benefits.