



CONFERENCE REPORT

Echinacea in Children

University Hospital Zurich (USZ)
Zurich, Switzerland
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A.Vogel

Introduction

Children experience 6 to 8 respiratory tract infections (RTIs) annually and a high proportion of illnesses (~30 %) progress to complications such as *sinusitis*, *otitis media*, *bronchitis* or *pneumonia* ^[1]. The latter conditions often represent bacterial superinfections of originally viral illnesses. RTIs are therefore the number one reason for prescription of antibiotics, which further increase susceptibility to infections – a vicious circle, as illustrated in Figure 1 ^[2-4].

From autumn to spring, a few children fall from one infection into the next ^[5]. Desperate parents seek for medical advice only to learn that there is nothing to worry about. Technically, even up to eight episodes are not an indicator for underlying immune dysfunction in young children ^[6]. This however does not solve the concern of parents, who turn away, looking for immune boosters on the internet, where there is plenty to find...

Parents thus rely on supplements, vitamins and alternative therapies in the sense of '*primum nil nocere*'. Their use often remains empirical and is devoid of any scientific evidence ^[7,8]. Prior to their recommendation, products would have to pass open, controlled field-studies under real-life conditions. They will have to satisfy parent's needs, be cost-effective, safe and most importantly, the children need to love it for good compliance – a real challenge.

Echinacea purpurea has previously been shown to prevent viral infections in adults. It is most effective in those with high risk of infection and therefore our latest research focussed on the most susceptible segment of our population - children ^[9-11]. A children-friendly formulation was especially developed for this purpose (Echinaforce® Junior tablets containing 400mg of EF extract*) and was subjected to scientific investigations.

This conference discusses the novel evidence for the use of *Echinacea* in children. It examines if the new pediatric formulation Echinaforce® Junior tablets could have the potential to control respiratory tract infections and maybe the need for antibiotics in this population. A dose-response clinical trial and a new mode-of-action are to address questions of effective concentrations and pharmacology of EF extract in children.

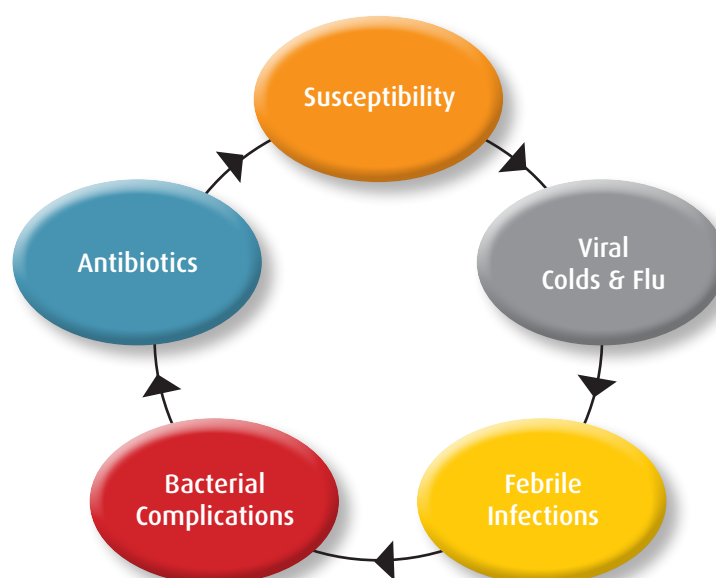


Figure 1: Children are susceptible to respiratory tract infections (RTIs), which tend to develop into bacterial complications requiring antibiotics. These further increase the susceptibility to infections – a vicious cycle.

*Echinaforce® Junior tablets contain 400 mg hydroalcoholic extract from freshly-harvested *Echinacea purpurea* (95% herba and 5% root).

Echinacea Prevents Bacterial Superinfections

Dr. Ross Walton, Therapeutic Frontier, Imperial College, London (UK)

In children, viral infections have a tendency to develop into bacterial superinfections such as *otitis media*, *bronchitis*, *sinusitis* or *pneumonia*. The expression of ICAM-1 receptor on infected epithelium plays an important role in attraction of bacteria for subsequent super-infection. *Respiratory syncytial virus* (RSV), *influenza* and *Streptococcus pneumoniae* are notorious and often lethal infection partners in children^[12].

We cultivated bronchial epithelial cells from a 6-year old boy and infected the tissue with RSV or influenza virus *in vitro*^[13]. After 48 hours, a clinical isolate of *S. pneumoniae* (*pneumococcus*) was added to measure adherence (super-infection, Figure 2). EF extract significantly reduced the attraction of *S. pneumoniae* after viral infection via down-regulation of ICAM-1 receptor as shown by immunocytochemical staining (Figure 3 C and D in comparison with B).

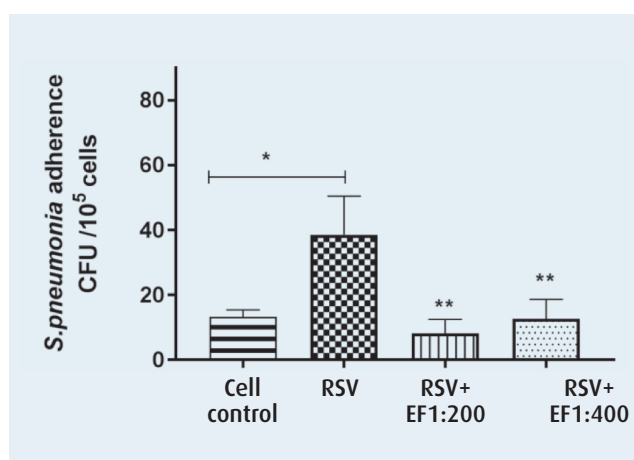


Figure 2: RSV infection significantly increased *S. pneumoniae* adherence to airway epithelium (* $p < 0.05$, ** $p < 0.01$). Post-infectious treatment with EF extract significantly reversed this pathological process, whereas results with influenza were very similar (data not shown).

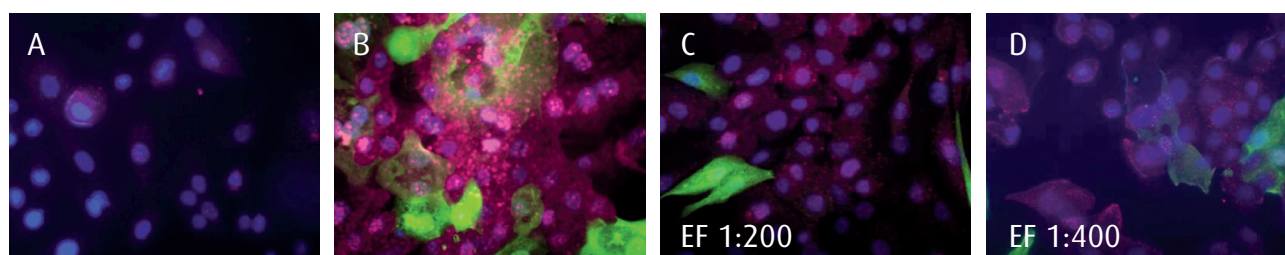


Figure 3 A – D: Juvenile bronchial epithelial cells with nuclei stained in violet. RSV infection (green) induced bacteria-binding ICAM-1 (magenta), which was dose-dependently reversed by EF extract (1:200 [C] and 1:400 [D]).

Echinacea prevents bacterial super-infections through down-regulation of ICAM-1 receptors on virally infected juvenile epithelium. The mode of action in children is highly similar to that in adults. It applies to both, RSV and influenza infections, which are the most frequent triggers of complications and antibiotic prescriptions in this population^[14].

Echinacea for the Treatment of Acute Respiratory Tract Infections: A Dose-Response Clinical Trial

Dr. Simon Feldhaus Paramed Ambulatory Centre, Baar (CH)

Cold remedies in children are strongly restricted today, mostly due to lack of efficacy or safety issues. Age limits of cough medicines were adjusted, decongestants have reported rebound effects and anti-inflammatory agents are discussed to increase rather than prevent complications^[15]. Initial symptom relief may be desirable but effective recovery and the prevention of complications are equally important.

This clinical study involved children aged 4 – 12 years, which were recruited by 10 Swiss pediatric practices. 1200 or 2000 mg EF extract (3 or 5 Echinaforce® Junior tablets, EFJ) were randomly applied for the treatment of acute cold symptoms. Up to three episodes were medicated for a maximum of 10 days^[16].

A total of 130 cold episodes occurred in 79 children during the 5.3 months of observation. Dose-increase from 1200 to 2000 mg EF extract shortened episode duration from 8.1 ± 3.5 to 6.9 ± 3.4 days (ITT collective, $p < 0.05$, Figure 4). Correcting for effective compliance further enhanced the treatment effect from $\Delta = 1.2$ to 1.7 days ($p=0.020$).

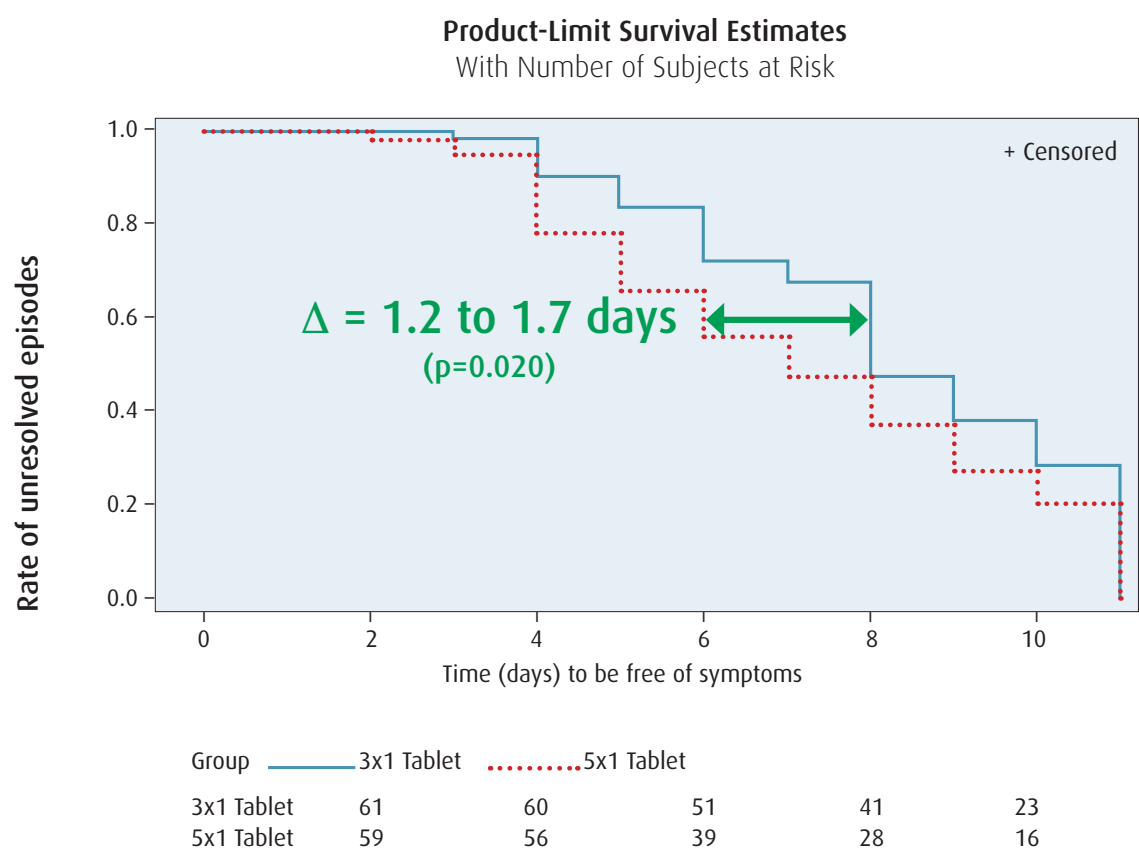


Figure 4: Time to symptom resolution by Kaplan-Meier curve (blue line = 1200mg, red line = 2000mg).

After 10 days treatment only 8.7% of episodes remained unresolved in the group taking the 2000 mg dose in comparison with 23.5% with 1200 mg of EF extract ($p=0.005$). Dosage of 2000 mg decreased the risk of recurrent infections from 71.9% to 58.1% and the overall cold incidence from 3.6 episodes (as per history) to 1.8 episodes in susceptible children ($p<0.001$).

Tolerability of EFJ was rated by 98.5% of physicians and 99.2% of parents as “good” or “very good”. Thirteen (13) children (19.1%) reported adverse events but none was causally related to EFJ or serious. Finally, over 80% of parents stated that they would want to take the medicament again.

An increased dose of EF extract (2000mg) is significantly more effective in reducing acute cold symptoms in children than lower doses. Effective symptom resolution is achieved after the first day of treatment and at 10 days, 9 out of 10 episodes are fully resolved. Fewer recurrences lead to a reduced cold incidence over time and finally the safety of both dosage regimen was exceptionally good.

ACUTE TREATMENT WITH ECHINAFORCE® JUNIOR TABLETS

- RTIs, especially coughing often are prolonged in children
- Fast recovery is desirable to avoid recurrences/complications
- 2000 mg EF extract shortens RTI episodes by 1.2 – 1.7 days
- 9 out of 10 episodes are fully resolved after 10 days and
- Fewer recurrences result in children treated with EFJ



Prevention of Respiratory Tract Infections with *Echinacea* in Children 4–12 Years Old

Dr. Mercedes Ogal, Pediatric Specialist, Pediatric Clinic, Brunnen (CH)

Effective prevention of RTIs in children has far-reaching benefits including the reduction of RTI complications and maybe of antibiotic prescriptions. Many parents rely on vitamins and food supplements with unknown efficacy and safety profile in this population.

The aim of this randomized, controlled and blinded study was to investigate safety and efficacy of Echinaforce® Junior tablets for the long-term prevention of RTIs over 4 months^[17]. 203 children aged 4 – 12 years were recruited by 13 general and pediatric practices in Switzerland. N=103 children were randomly allocated to daily 3 x 1 Echinaforce® Junior tablet (EFJ 400mg) and N=98 to 3 x 1 vitamin C tablet (VC 50mg) for control. Nasal secretions were collected during acute infections and screened for respiratory pathogens using RT-PCR (Allplex®).

The majority of children using EFJ remained free of RTIs and reported 32.5% fewer cold and flu episodes than the control group (odds ratio OR=0.54 [95% CI, 0.31-0.94], $p = 0.030$). Overall, 429 cold days occurred with EFJ in comparison to 602 days with VC ($p < 0.001$). Four children (3.9%) with EFJ required antibiotics on 31 days in comparison to 14 prescriptions in the VC group (14.3%) administered over 111 days, as shown in Figure 5 (72.7% reduction, $p < 0.001$).

The reduction in use of antibiotics was associated with a marked, 63.8% prevention of bacterial infections and of RTI complications (*pneumonia*, *tonsillitis* or *otitis media*), where 9.7% and 20.4% of children experienced 11 and 29 events with EFJ and control, respectively ($p < 0.05$). A significant reduction of influenza (3 vs. 20 detections, $p < 0.05$) and of membranous virus infections overall (28 vs 47 detections, $p < 0.05$) was further found for *Echinacea*.

In those where respiratory symptoms still occurred, these were less severe and episodes were shorter by 1.4 days with EFJ compared to control treatment. Fever (i.e. body temperature $\geq 37.8^{\circ}\text{C}$) occurred on 1.6 vs. 4.9 days on average, showing a 67.3% reduction (3.3 days) in those using EFJ ($p < 0.001$, Figure 5).

EFJ was non-inferior to VC with respect of safety, whereas 36.9% and 41.8% of children experienced 51 (49.5%) and 78 (79.6%) adverse events.

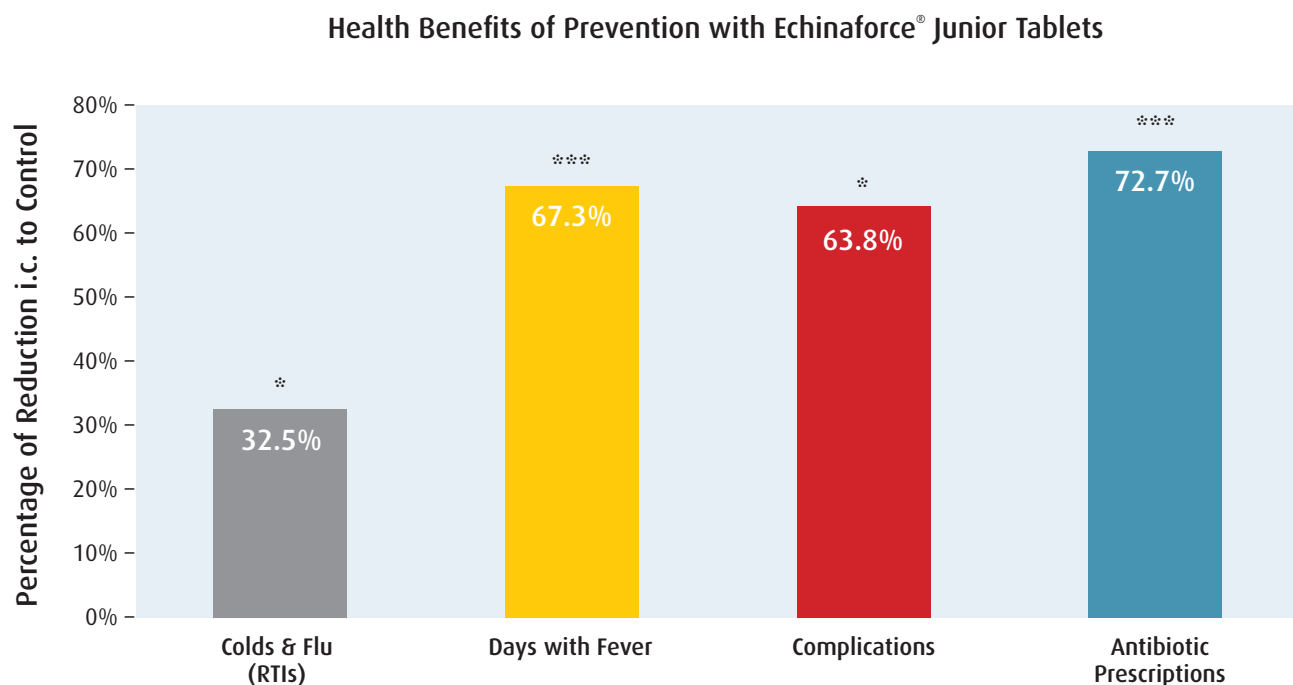


Figure 5: Children with EFJ benefited from prevention of multiple complaints, which are medically related (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

The results demonstrate significant health benefits in children using EFJ, which include the principal prevention of RTIs but also the reduction of secondary complications. EFJ significantly prevented membranous virus infections such as influenza, which has already been seen in adults^[9]. Children demonstrate more robustness and a noticeably increased immune resistance to finally end in a significantly reduced need for antibiotic prescriptions (Figure 6)

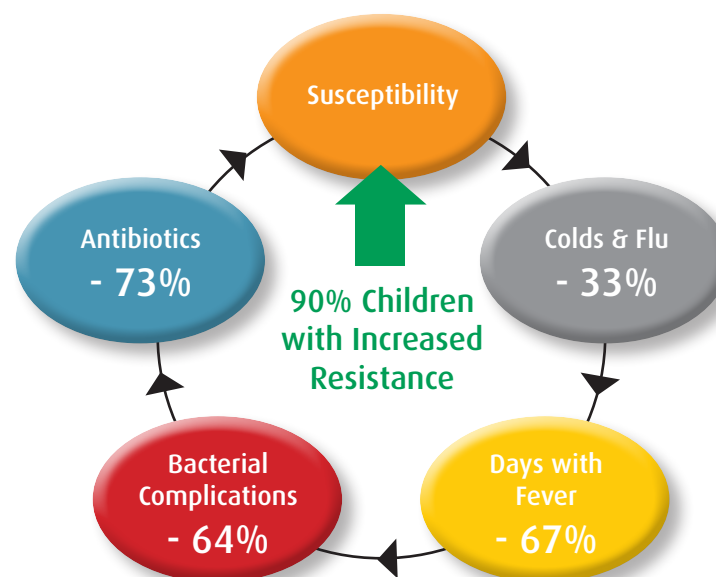


Figure 6: EFJ significantly increased the resistance in 9 of 10 children and produced benefits on various levels (given in percentages). Obviously, EFJ interrupts the vicious circle of infections leading to complications, antibiotics and further susceptibility to infections.

Conclusion

Respiratory tract infections (RTIs) produce a tremendous pressure on the health care provider to dispense antibiotics as a result of parent's expectations and the difficulty in clinically differentiating viral from bacterial etiology^[18]. Experiencing severe illness in their child, parents have little sympathy with the WHO's recommendations to reduce antibiotics.

Prevention of RTIs could effectively solve the dilemma beforehand and EF extract (Echinaforce®) has been shown to work in adults - evidence in children was lacking so far.

Data presented at this conference provides solid evidence for the use of EF extract in children nowadays. With Echinaforce® Junior tablets (EFJ) a children-friendly formulation is available that shows a high level of safety, acceptance and compliance.

The use of 1200 mg EF extract from freshly harvested *Echinacea purpurea* is effective and safe for the long-term prevention in children: The immune resistance is noticeably improved as manifested in a reduced number of respiratory tract infections, *otitis media*, *pneumonia* or *tonsillitis* (complications). In consequence, antibiotic prescriptions with EFJ are significantly reduced.

For the treatment of acute respiratory symptoms 2000 mg EF extract is more effective than a daily dose of 1200 mg. Episodes are shortened by 1.2 to 1.7 days and a higher proportion of children recover after 10 days of treatment.

Pharmacodynamic actions of EF extract in children principally resemble those in adults and include potent antiviral effects and support of immune functions. At acute stages, EF reduces the expression of bacteria-binding receptors (ICAM-1) and the development of super-infections on epithelium. It shows a specificity against membranous viruses such as RSV, *parainfluenza* and *influenza*, which are predominantly active in the first 5 years of life. This implicates the importance of EFJ also for this very young population.

Overall, Echinaforce® Junior tablets were demonstrated to be efficacious for the real-life needs. They comply with the demands of parents and children, showing a high level of acceptance and safety. Pediatricians should consider EFJ as a valuable option for prevention and treatment of respiratory tract infections in their young clients and maybe as alternative for just calming down their parents.

ECHINAFORCE® JUNIOR TABLETS IN CHILDREN

- Echinaforce® Junior tablets are a children-friendly *Echinacea* formulation
- With **antiviral** and **immune-modulatory** action
- Safe & effective for **prevention and treatment of RTIs**
- Effective in **preventing RTI complications** and **reducing antibiotics**
- Effective in the **treatment of acute symptoms** if they still occur

Expert Panel



Dr. Peter Fisher

Royal London Hospital for Integrated Medicine, London (UK)

Peter Fisher is Director of Research at the Royal London Hospital for Integrated Medicine (RLHIM), part of the University College London Hospitals. He is also Physician to Her Majesty Queen Elizabeth II. He is a member of the WHO's Expert Advisory Panel on Traditional, Complementary and Integrative Medicine and a member of the Expert Reference panel of the UK National Institute of Health and Care Excellence (NICE). Peter Fisher's research work centres on responding to the problems in health care, including 'effectiveness gaps', multimorbidity and polypharmacy, by integrating the best of traditional and complementary medicine.



Dr. Mercedes Ogal

Pediatric Specialist, Paediatric Clinic, Brunnen (CH)

Mercedes Ogal is working as a specialized integrative pediatrician since 14 years in a pediatric medical practice in Central Switzerland. She developed her deep knowledge in complementary medicine since 1991 in phytotherapy, acupuncture, homeopathy, medical hypnosis and orthomolecular medicine and owns certificates in various medicinal disciplines. Furthermore Dr. Mercedes Ogal is author of publications and speaker on various national and international lectures and conferences.



Dr. Simon Feldhaus

Paramed Ambulatory Centre, Baar (CH)

Dr. Simon Feldhaus took his Medical Studies at the University of Saarland and is now a general practitioner in Switzerland. He graduated further as a natural health professional and owns a certificate of proficiency for phytotherapy. Since his employment as senior physician at the Aesculap clinic in Brunnen, he is now engaged at Paramed centre for complementary medicine. Furthermore, Dr. Feldhaus is author of various publications and has been speaker at national and international conferences.



Dr. Ross Walton

Therapeutic Frontier, Imperial College, London (UK)

Ross Walton attained his PhD from Imperial College investigating mechanism of respiratory viral induced modification of allergic airway responses. He has substantial experience with complex in vivo and human models of virus infection, including rhinovirus, respiratory syncytial virus and influenza. Employing state-of-the-art analytical approaches in patient samples alongside complimentary in vivo models, he explores the cellular interactions underpinning the immunological basis of chronic respiratory diseases and viral infection.

References

1. Aitken M, Taylor JA. Prevalence of clinical sinusitis in young children followed up by primary care paediatricians. *Arch Pediatr Adolesc Med.* 1998;152:244-248.
2. Schindler C, Krappweis J, Morgenstern I, Kirch W. Prescriptions of systemic antibiotics for children in Germany aged between 0 and 6 years. *Pharmacoepidemiol Drug Saf.* 2003;12(2):113-20.
3. Leowski J. Mortality from acute respiratory infections in children under 5 years of age: Global estimates. *World Health Statistics Quarterly.* 1986; 39:138-44.
4. Thackray LB, Handley SA, Gorman MJ, et al. Oral antibiotic treatment of mice exacerbates the disease severity of multiple flavivirus infections. *Cell* 2018;22(13):3440-3453.
5. Grüber C, Keil T, Kulig M, Roll S, Wahn U, Wahn V; MAS-90 Study Group. History of respiratory infections in the first 12 yr among children from a birth cohort. *Pediatr Allergy Immunol.* 2008 Sep;19(6):505-12
6. Jesenak M, Urbancikova I, Banovcin P. Recurrent Respiratory Infections in Children – Definition, diagnostic approach, treatment and prevention, in *Bronchitis*. Martin-Loeches I, Ed. (2011) 119-148, Intech Open Science, Rijeka, Croatia.
7. Soni MG, Thurmond TS, Miller ER, Spriggs T, Bendich A, Omaye ST. Safety of vitamins and minerals: controversies and perspective. *Toxicol Sci.* 2010;118(2):348-55.
8. Spiegelblatt L, Laine-Ammara G, Pless IB, Buyver A. The use of alternative medicine by children. *Pediatrics.* 1994;94:811-814.
9. Jawad M, Schoop R, Suter A, Klein P, Eccles R. Safety and Efficacy Profile of Echinacea purpurea to Prevent Common Cold Episodes: A Randomized, Double-Blind, Placebo-Controlled Trial. *Evidence-Based Complementary and Alternative Medicine.* 2012 doi:10.1155/2012/841315.
10. Schapowal A. Efficacy and safety of Echinaforce® in respiratory tract infections. *Wien Med Wochenschr.* 2013;163(3-4):102-5.
11. Pleschka S, Stein M, Schoop R, Hudson JB. Anti-viral properties and mode of action of standardized Echinacea purpurea extract against highly pathogenic avian influenza virus (H5N1, H7N7) and swine-origin H1N1 (S-OIV). *Virology Journal* 2009;6:197.
12. Claire M. Smith, Sara Sandrini, Sumit Datta, et al. Respiratory Syncytial Virus Increases the Virulence of Streptococcus pneumoniae by Binding to Penicillin Binding Protein 1a A New Paradigm in Respiratory Infection. *Am J Respir Crit Care Med.* 2014 Jul 15;190(2):196-207.
13. Vimalanathan Selvarani, Schoop Roland, Suter Andy. Echinacea purpurea extract can reverse respiratory virus induced secondary bacterial infection. GA Conference (Poster), 3rd Sept, Basel, Switzerland.
14. Vimalanathan S, Schoop R, Suter A, Hudson J. Prevention of influenza virus induced bacterial superinfection by standardized Echinacea purpurea, via regulation of surface receptor expression in human bronchial epithelial cells. *Virus Research* 2017;233:51-59
15. Little P, Moore M, Williamson I, Leydon G, McDermott L, Mullee M, Stuart B. Ibuprofen, paracetamol and steam for patients with respiratory tract infections in primary care: pragmatic randomized factorial trial. *BMJ.* 2013;347:1-13.
16. Bächler A, Feldhaus S, Lang G, Klein P, Suter A, Schoop R. Dose-dependency of Echinacea in the treatment of acute common colds in children 4 – 12 years. Société Suisse de Pédiatrie (SSP, Poster), 24th May, Lausanne, Switzerland.
17. Ogal M, Klein P, Schoop R. Echinacea for the Prevention of Respiratory Tract Infections in Children 4 - 12 years: A Randomized, Blind and Controlled Study. Société Suisse de Pédiatrie (SSP, Poster), 24th May, Lausanne, Switzerland.
18. Arroll B. Antibiotics for upper respiratory tract infections: an overview of Cochrane reviews. *Respiratory Medicine* 2005;99:255-261.

Echinaforce® Junior Tablets

Echinaforce® Junior tablets contain 400 mg hydroalcoholic extract from freshly-harvested *Echinacea purpurea* (95% herba and 5% root).

- ✓ Antiviral & Immunomodulatory
- ✓ Made from fresh organically grown Echinacea plant
- ✓ Patented Pediatric Formulation
- ✓ Approved Pediatric Posology
- ✓ Tooth-friendly

