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Oleaceae Pollen Allergy and its Cross-Reactivity in the Mediterranean Area in the Context of Globalization

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ABSTRACT

Opening frontiers has led in the last two decades to a massive migration of Romanians to Spain and Italy, two countries known to have large areas planted with olives. Romania owns large areas planted with ash forests. Because of cross-reactivity between these two trees belonging to the *Oleaceae* family and the big allergenic potential of olive pollens, after a number of years of residence in these countries, many Romanians will present allergic respiratory symptoms of rhinitis and asthma, both in the season of olive pollination and ash pollination.

Keywords: Cross Reaction; Italy; Oleaceae; Pollen; Romania; Spain

INTRODUCTION

Oleaceae is a basal family belonging to the monophyletic order Lamiales.[1] *Oleaceae* family includes about 400 tree species, which can grow spontaneous or can be planted for ornamental, medicinal or food purposes.[2] The family is distributed on all continents except the Antarctic, from northern temperate to southern subtropical regions and from low to high elevations. Some genera are widespread and occur on more than one continent.[3] These species are mostly entomophilus (having limited allergic relevancy), while species of *Oleae, Ligustrum*, *Fraxinus* and *Syringa* have clinical importance, with *Oleae* europaea being the most important.[1] The olive (Olea europaea) is cultivated for its fruit and oil, species of Fraxinus are grown for timber, and Syringa, and Ligustrum are planted as ornamentals.[3]

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Olive Biology and Clinics

The Mediterranean Sea area represents the leading producer of olive oil. The most important countries in this industry are Spain, Italy, Greece, Portugal, Tunisia, Turkey, and some other European Union members. Olive orchards can reach big city suburbs; in some countries they can occupy half of the agricultural lands. In the last years, due to the agricultural policies of the European Union, there was a tendency to increase the areas planted with olive trees, especially in regions where other types of plants had been initially cultivated.[4] The season of olive pollen (*Olea europea*) begins late in April and ends in early June, reaching its maximum around the middle and end of May.[4,5] Diurnal fluctuation in pollen concentration shows consistent release throughout the day and night, but with a slight peak between 2-6 PM. While primarily insect-pollinated, *O. europaea* pollen is very light and buoyant, and therefore, large amounts are airborne.[1] Pollen's density can present major diversity, depending on climate, vegetation and ground, with a certain degree of variation between East and West Mediterranean, coastal and inland regions,

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provinces situated at the same latitude (for example Cordoba versus Sicily) and from one year to another. Olive species from the inland of the continent (Cordoba region) are more vulnerable to climatic variation (frost-defrost) than the species cultivated in the coastal regions (Sicily) with more stable climatic conditions. Bloom and accordingly pollination periods are earlier in Sicily when compared to the Cordoba region. Differences have also been observed between olives which grew in the same geographical region but at a different altitude.[6]

Spain possessed in 2007 according to Eurostat informations 2,47 millions hectares(ha), with 350.000 ha increasing since 1991, most important regions occupied with olive orchards being Jaen, Cordoba, Seville, Ciudad Real, Toledo, Badajoz and Andaluzia.[7] Italy possessed in 2007 aproximatly 1,2 mil ha olive orchards[7] with the biggest areas in Puglia, followed by Calabria and Sicily; get together these 3 provinces cover 60% of olive oil production of Italy. In the northern Italy areas with important olive orchards are, in order, Tuscany (about 108 000 ha), Lazio (about 87 000 ha), Campania (about 81 000 ha), and Abruzzo (about 44 000 ha).[8] Greece has 800.000 ha of olives, mainly in semi-mountainous and coastal areas (Crete, Peloponnese) and Portugal 379.000 ha. Tunisia has 1,69 million ha of olive groves and Turkey 815.000.[7]

Oleaceae pollen presents an important allergic potential, representing one of the most important causes of respiratory allergies in Mediterranean area.[9] The extract of olive pollen contains at least 20 protein bands with allergenic reactivity.[10,11] Olive pollen contains 12 allergens, classified from Ole e 1 to Ole e 12.[11] The most frequent allergen is Ole e 1, which is reported to cause clinical symptoms in 70% of olive pollen allergic patients, thus being considered the major allergen. This allergen contributes significantly to the total allergenicity of Oleaceae pollen extract and its concentration is closely related to the allergenic reactivity of the entire pollen extract. Ole e 1 was the first allergen discovered in olive pollen. Ole e 1 is an acidic heterogeneous protein that exhibits 2 variants: a glycosylated form (20 kDa) and a nonglycosylated one (18,5 kDa) of the same 145 polypeptide chain.[10-13] Its function is still unknown; at present there are 2 hypothesis: reproductive function or the control of the osmotic gradient in the hydration process.[11] Besides Ole e 1, further 11 additional olive pollen allergens have been described following purification from the *Olea europea* pollen extract.[11] Ole e 2 is a significant allergen and belongs to the profilin family. Profilin is a ubiquitos protein that controls actin polymerization in eukaryotic cells from vegetable and animal biological sources. Because of high cross-reactivity between profilins and the wide distribution they are considered pan-allergens. Ole e 2 displays high cross-reactivity, showing structural and immunological similarity with other pollen sources such as birch, ash, and grass. The prevalence of this allergen was estimated between 24 and 27% in olive allergic patients and its presence was related to the risk of developing asthma.[11] Ole e 3 is a pocalcin belonging to the Ca^{2+} - binding protein subfamily. The prevalence varies between 20 and 50% in olive allergic patients, depending on the geographical area. Ole e 3 has a lower cross-reactivity than Ole e 2 with pollens from rapeseed, Bermuda grass, and birch.[11] Ole e 4 shows IgE binding capacity and has no homology with any known protein. Ole e 5 is a superoxide dismutase (SOD), recognized by 39% of pollen allergic patients. It shows 90% homology with other SOD from several plant species. Ole e 5 was found in the olive fruit pulp and this could be an explanation for cross allergy between olive pollen allergy and olive fruit allergy. Ole e 6 is the smallest allergen, recognized by 50% of allergic patients and without homology with other proteins. Ole e 7 shows similarities with nonspecific lipid transfer proteins (LTP) from plant tissues. Ole e 7 was found in 47% of allergic patients and its presence was associated with an increased risk of food anaphylaxis, depending on the geographical area. Ole e 8 is a calcium-binding protein with a very low prevalence. Ole e 9 is a glycosylated -1, 3-glucanase, which belongs to the pathogenesis-related (PR-2) protein family, has the highest molecular mass from olive pollen allergens and a low concentration in olive pollen. Ole e 10 is considered a major allergen, presents cross-reactivity with proteins from various pollens (Oleaceae, Gramineae, Chenopodiaceae, Cupressaceae, Ambrosia and Parietaria) and is associated with severe asthma. Ole e 11 is a pectin methylestrase recently detected and Ole e 12 belongs to the family of the isoflavone reductases.[11] Value limits for olive pollen's density to provoke symptoms are 162 grains/m^3 (equivalent to 22.7 ng of olive pollen allergen/m^3 or 0.9 ng/m^3 of Ole e 1).[10] The sensitization rate in the Mediterranean areas covered with important olive orchards is comparable to those for gramineae.[14] Olive pollen allergy is among the first three sensitizations in Italy[15] and the second in Spain as a whole, while being in the first place in the southern

provinces, with incidences exceeding 20% for prick tests.[16] Olive pollen density can reach in some Spanish provinces up to 14.000 grains/m^3 (Andalusia),[17] which, alongside a higher frequency of symptoms of rhinitis and asthma among the inhabitants of that region, has led to the term "special olive pollen sensitization", causing an important consequence for public health.[10] The clinical picture of *Oleaceae* pollen allergy is dominated by symptoms of rhinitis or rhinoconjunctivitis (nasal itching, sneezing, obstruction, discharge, tearing), followed or associated by symptoms of asthma (wheezing, cough, chest tightness, shortness of breath),[10,18,19] with a higher incidence in adults.[11] Allergic symptoms have been also reported after the pollination season is over.[18]

Ash Biology and Clinics

Ash is a European native tree with a large distribution on the entire continent, from Ireland to the Russian Federation and from southern Scandinavia to southern Europe (Spain, Italy, the Balkans).[20] Ash is the principal member of the Oleaceae family in Romania. Ash trees can be found in forests, riverside coppices, meadows, at altitudes ranging from those of plains, including the Danube Delta, to that of inferior mountain regions. Ash forests are called *frasinete* (*Fraxinetum*). *Fraxinetum* are rather rare and don't have a specific area. In forests, ash grows mainly among other trees (oak, elm, alder, maple, and hawthorn) in areas characterized by a permanent excess of humidity. The ash pollination season is between March and May.[21] Exposure to ash pollen is higher in rural areas than in urban areas[22] and 50% of total daily pollen was noted at 14:00.[23] Ash pollen contains 3 allergens, out of which sensitivity to Fra e 1 is found in approximately 80% of the patients tested positive at prick tests, thus being considered the major alergen. An important study made in Austria between 1997 and 1999 has diagnosted the sensitization to ash pollen in ~18% of pollen-allergic patients.[20] Until now, this is the biggest study realized in Europe regarding the prevalence of ash pollen allergy.

Privet and lilac Biology and Clinics

The genus Ligustrum contains about thirty-five species of deciduous or evergreen shrubs native to Europe, Northern Africa, Asia, and Australia. Common privet, *L. vulgare*, is widely distributed through almost all of Europe. Privets grow along woodland edges, in floodplains, and riparian forests. Common privet is a deciduous or semi-evergreen shrub with height and spread of 3 m. Pollination season is between May and June. Despite being primarily insect-pollinated, privets are facultatively anemophilous.[4] The major allergen is Lig v 1, with important cross-reactivity with Ole e 1.[25] Sensitization can easily be demonstrated and skin test positivity to olive in an olive and ash-free area has been attributed to privet.[24,26,27]

Syringa vulgaris (lilac or common lilac) is a species of flowering plant in the family Oleaceae, native to the Balkan Peninsula, where it grows on rocky hills. The major allergen is Syr v 1 which presents important cross-reactivity with Ole e 1.[28] Until now, this cross-reactivity was very little studied in clinical studies.

Cross-reactivity in the *Oleaceae* Family

Cross-reactivity between the major allergens (Ole e 1, Fra e 1) of these 2 trees is important, reaching 85%-95% due to the considerable amino-acid sequence identity and immunologic cross-reactivity.[29-31] An important clinical argument for this comes from Turkey, in the region of Anatolia, a part of the country without olive trees, but with important ash forests nearby; 2 studies realised in Ankara and Eskisehir have indicated a degree of sensitization to *Oleae* pollen of 60% for Ankara[32] and 22% for Eskisehir.[33] Arguments come also from a small study which showed 14 positive skin tests to Ole e 1, Fra e 1, Lig v 1 and Syr v1 from 15 olive-monosensitized patients[29] and from an earlier study[34]. Most of the studies published until now about *Oleaceae* pollen allergy used extracts for olive, much less extracts for ash and very few privet extracts. Therefore, it is difficult to conclude with high precision about the primary sensitization in patients, especially in cases where we can find in the same region 2 or more of the species detailed before. An older article which studied the cross-reactivity between pollen extracts of four species of *Oleaceae* (olive, ash, privet, lilac) suggested that only *O. europaea* extract should be used in diagnosis in Oleaceae pollen allergy.[35]

Cross-reactivity with other Plant Species

In the previous years, several studies have demonstrated cross-reactions between allergens from olive pollen and allergens from other plant species pollens. Ole e 1 shows partial structural similarities and various cross-reactivity with Che a 1,[29,36] Phl p 11,[37] Pla l 1[29,38] and Sal k 5 (unpublished data). This cross-reactivity for a part of olive pollen allergens (Ole e 1,

Ole e 2, Ole e 3, Ole e 10), demonstrated in laboratory studies, shall need confirmation in future clinical studies.

Therapeutical Aspects

Respiratory allergy to olive pollen has a specific treatment: immunotherapy. This can be administrated subcutaneous[39] or sublingual,[40] with natural allergenic extracts or allergoids with favorable results. Recent experimental studies that used various peptides have suggested the possibility of using some Ole e 1 peptides as a safe vaccine candidate for immunotherapy of Oleaceae pollen allergy.[41] In the case of cross-reactivity, the best option is represented by the personalized treatment.

Romanians in the Mediterranean Area

The last decade meant for more than two million Romanians leaving their country in order to work abroad, especially in Italy and Spain, countries with big plantation of olives. A significant part of Romanians who went to work in Spain has worked or is still working in agriculture, picking olives or in constructions, an occupation with daily exposure to pollens. According to the latest official estimates, over 700,000 Romanians live and work legally in Spain, however unofficial figures indicate about more than 1 million Romanian citizens living in Spain. Areas with big Romanian communities are Madrid, Huelva, Castellon, Alcala de Henares, many of them having big areas planted with olives.[42] Another important Romanian community lives in Italy, approximately 900,000 according to official records, with large groups living in the southern provinces (Sicily, Sardinia, Calabria, Basilicata) and northern provinces (Piedmont, Lombardy, Tuscany, Umbria, Lazio).[43] The majority of these persons have arrived in Spain and Italy between 2000-2005, thereby being exposed for a period of time enough to be sensitized to *Oleaceae* pollen.

CONCLUSION

As we have shown above, the prevalence of *Olea europaea* pollen allergy is significant in regions where Romanians work and live, especially in the case of Spain and Italy. Because of the long time presence of Romanians in these regions, there is a high probability for a part of them to acquire over the years a sensitization at *Oleaceae* pollen. According to observations made for other countries, which were confronted with a massive wave of work migration, a lot of the migrants will return to their home countries after a number of years. In the situation discussed above, an important part of those who will come back will be sensitized to *Oleaceae* pollen. This sensitization will call for the introduction in the routine testing in Romania for *Oleaceae* pollen and particularly for *Fraxinus excelsior* pollen, because of the cross-reactivity between the main allergens presented in the pollens Fra e 1 and Ole e 1. This material is a review of English articles regarding *Oleaceae* pollen allergy and presents a hypothesis which shall need confirmation from a future partnership between allergists from Romania, Italy and Spain.

Competing Interests

The author declares that he has no competing financial interests.

REFERENCES

1. Weber RW. Allergen of the month-European olive. Ann Allergy Asthma Immunol 2013; 110(4):A19.
2. Bousquet J, Guérin B, Hewitt B, Lim S, Michel FB. Allergy in the Mediterranean area. III: Cross reactivity among Oleaceae pollens. Clin Allergy 1985; 15(5):439-48.
3. Wallander E, Albert VA. Phylogeny and classification of Oleaceae based on rps16 and trnL-F sequence data. Am J Bot 2000; 87(12):1827-41.
4. Orlandi F, Vazquez LM, Ruga L, Bonofiglio T, Fornaciari M, Garcia-Mozo H, et al. Bioclimatic requirements for olive flowering in two Mediterranean regions located at the same latitude (Andalucia, Spain and Sicily, Italy). Ann Agric Environ Med 2005; 12(1):47-52.
5. Bonofiglio T, Orlandi F, Ruga L, Romano B, Fornaciari M**.** Climate change impact on the olive pollen season in Mediterranean areas of Italy: air quality in late spring from an allergenic point of view. Environ Monit Assess 2013; 185(1):877-90.
6. Alché JD, Castro AJ, Jiménez-López JC, Morales S, Zafra A, Hamman-Khalifa AM, et al. Differential characteristics of olive pollen from different cultivars: biological and clinical implications.J Investig Allergol Clin Immunol 2007; 17 (Suppl 1):17-23.
7. Gabriella Camarsa, Stephen Gardner, Wendy Jones, Jon Eldridge, Tim Hudson, Edward Thorpe, Eamon O'Hara (AEIDL, Communications Team Coordinator). Four main olive producing countries in: LIFE among the olives Good practice in improving environmental performance in the

olive oil sector European Commission Environment Directorate-General, 10-11.
8. G Fontanazza. Importance of olive-oil production in Italy. In: Integrated Soil and Water Management for Orchard Development: Role and Importance. Proceedings of the International Seminar "The Role and Importance of Integrated Soil and Water Management for Orchard Development" Organized by the FAO Land and Water Development Division and the College of Agricultural Sciences, University of Teramo, Italy, 2004: 9-10. FAO LAND AND WATER BULLETIN 10, 13-20.
9. García BE, Lizaso MT, Moreno C, Rodríguez R, Villalba MT, Ledesma A, et al. Oleaceae-induced pollinosis in an area with exposure to olive and ash trees. J Investig Allergol Clin Immunol 2011; 21(1):34-7.
10. Cárdaba B, Llanes E, Chacártegui M, Sastre B, López E, Mollá R, et al. Modulation of allergic response by gene-environment interaction: olive pollen allergy. J Investig Allergol Clin Immunol 2007; 17 (Suppl 1):31-5.
11. Esteve C, Montealegre C, Marina ML, García MC. Analysis of olive allergens. Talanta 2012; 92:1-14.
12. Quiralte J, Palacios L, Rodríguez R, Cárdaba B, Arias de Saavedra JM, Villalba M, Florido JF, Lahoz C. Modelling diseases: the allergens of Olea europaea pollen. J Investig Allergol Clin Immunol 2007; 17(Suppl 1):24-30.
13. Soleimani A, Morales S, Jimenez-Lopez JC, Castro AJ, Rodríguez-García MI, de Dios Alché J. Differential Expression and Sequence Polymorphism of the Olive Pollen Allergen Ole e 1 in Two Iranian Cultivars. Iran J Allergy Asthma Immunol 2013; 12(1):18-28.
14. Carnés J, Fernández-Caldas E. Ole e 4 and Ole e 5, important allergens of Olea europaea. Allergy 2002; 57(Suppl 71):24-8
15. Milani M**,** Pecora S; Rainbow Study Investigator Group. Clinical relevance of non-grass pollens respiratory allergies in Italy and effects of specific sublingual immunotherapy: The Rainbow Trial, a multicentre 3-year prospective observational study. Eur Ann Allergy Clin Immunol 2011; 43(4):111-6.
16. Rodríguez R, Villalba M, Batanero E, Palomares O, Quiralte J, Salamanca G, et al. Olive pollen recombinant allergens: value in diagnosis and immunotherapy. J Investig Allergol Clin Immunol 2007; 17 (Suppl 1):4-10.
17. Barber D, Moreno C, Ledesma A, Serrano P, Galán A, Villalba M, Guerra F, Lombardero M, Rodríguez R: Degree of olive pollen exposure and sensitization patterns. Clinical implications. J Investig Allergol Clin Immunol 2007; 17 (Suppl 1):11-6.
18. Kirmaz C, Yuksel H, Bayrak P, Yilmaz O. Symptoms of the olive pollen allergy: do they really occur only in the pollination season? J Investig Allergol Clin Immunol 2005; 15(2):140-5.
19. Skitarelić N, Skitarelić N. Hypersensitivity to the pollen of Olea europea in the Mediterranean area. Arh Hig Rada Toksikol 2009; 60(2):259-60.
20. Hemmer W, Focke M, Wantke F, Götz M, Jarisch R, Jäger S, et al. Ash (Fraxinus excelsior)-pollen allergy in central Europe: specific role of pollen panallergens and the major allergen of ash pollen, Fra e 1. Allergy 2000; 55(10):923-30.
21. Stancioiu PT, Lazar G, Tudoran GM, Candrea SB, Predoiu G, Sofletea N. Paduri aluviale cu Alnus glutinosa si Fraxinus excelsior (Alno padidon,Alnion incanae,Salicion albae)-91-E0*. Paduri de lunca mixte cu Quecus robur, Ulmus minor, Ulmus laevis, Fraxinus excelsior sau Fraxinus angustifolia din lungul marilor rauri-91F0. in: Habitate forestiere de interes comunitar incluse in proiectul LIFE/05/NAT/RO/0001876: habitate prioritare alpine, subalpine si forestire din Romania: masuri de gospodarire. Editura Universitatii “Transilvania” din Brasov, 2008:57-86.
22. Bosch-Cano F, Bernard N, Sudre B, Gillet F, Thibaudon M, Richard H, et al. Human exposure to allergenic pollens: a comparasion between urban and rural areas. Environ Res 2011; 111(5):619-25.
23. Puc M. Influence of meteorological parameters and air pollution on hourly fluctuation of birch (Betula L.) and ash (Fraxinus L.) airborne pollen. Ann Agric Environ Med 2012; 19(4):660-5.
24. Weber RW. Allergen of the month-privet. Ann Allergy Asthma Immunol 2013; 111(2):A15.
25. Batanero E, Gonzalez De La Peña MA, Villalba M, Monsalve RI, Martin-Esteban M, Rodríguez R. Isolation, cDNA cloning and expression of Lig v 1, the major allergen from privet pollen. Clin Exp Allergy 1996; 26(12):1401-10.
26. Asero R. Analysis of hypersensitivity to oleaceae pollen in an olive-free and ash-free area by commercial pollen extracts and recombinant allergens. Eur Ann Allergy Clin Immunol 2011; 43(3):77-80.
27. Cariñanos P, Alcázar P, Galán C, Domínguez E. Privet pollen (Ligustrum sp.) as potential cause of pollinosis in the city of Cordoba, south-west Spain. Allergy 2002; 57(2):92-7.
28. Batanero E, Villalba M, López-Otín C, Rodríguez R. Isolation and characterization of an olive allergen-like protein from lilac pollen. Sequence analysis of three cDNA encoding protein isoforms. Eur J Biochem 1994;

221(1):187-93.
29. Lombardero M, Obispo T, Calabozo B, Lezaún A, Polo F, Barber D. Cross-reactivity between olive and other species. Role of Ole e 1-related proteins. Allergy 2002; 57(Suppl 71):29-34.
30. Niederberger V, Purohit A, Oster JP, Spitzauer S, Valenta R, Pauli G. The allergen profile of ash (Fraxinus excelsior) pollen: cross-reactivity with allergens from various plant species. Clin Exp Allergy 2002; 32(6):933-41.
31. Palomares O, Swoboda I, Villalba M, Balic N, Spitzauer S, Rodríguez R, et al. The major allergen of olive pollen Ole e 1 is a diagnostic marker for sensitization to Oleaceae. Int Arch Allergy Immunol 2006; 141(2):110-8
32. Berna Dursun A, Celik GE, Alan S, Münevver Pinar N, Mungan D, Misirligil Z: Regional pollen load: effect on sensitisation and clinical presentation of seasonal allergic rhinitis in patients living in Ankara, Turkey. Allergol Immunopathol (Madr) 2008; 36(6):371-8.
33. Harmanci E, Metintas E. The type of sensitization to pollens in allergic patients in Eskisehir (Anatolia), Turkey. Allergol Immunopathol (Madr) 2000; 28(2):63-6.
34. Pajarón MJ, Vila L, Prieto I, Resano A, Sanz ML, Oehling AK. Cross-reactivity of Olea europaea with other Oleaceae species in allergic rhinitis and bronchial asthma. Allergy 1997; 52(8):829-35.
35. Pajarón MJ, Vila L, Prieto I, Resano A, Sanz ML, Oehling AK. Cross-reactivity of Olea europaea with other Oleaceae species in allergic rhinitis and bronchial asthma. Allergy 1997; 52(8):829-35.
36. Barderas R, Villalba M, Lombardero M, Rodríguez R. Identification and characterization of Che a 1 allergen from Chenopodium album pollen. Int Arch Allergy Immunol 2002; 127(1):47-54.
37. Marknell DeWitt A, Niederberger V, Lehtonen P, Spitzauer S, Sperr WR, Valent P, et al. Molecular and immunological characterization of a novel timothy grass (Phleum pratense) pollen allergen, Phl p 11. Clin Exp Allergy 2002; 32(9):1329-40.
38. Calabozo B, Díaz-Perales A, Salcedo G, Barber D, Polo F. Cloning and expression of biologically active Plantago lanceolata pollen allergen Pla l 1 in the yeast Pichia pastoris. Biochem J 2003; 372(Pt 3):889-96.
39. Moreno C, Fernández-Távora L, Acero S, Alonso MD, Barahona MJ, Blanco R, et al. Tolerance of a cluster schedule on the treatment of seasonal allergic respiratory disease with pollen extracts quantified in mass units. J Investig Allergol Clin Immunol 2003; 13(4):221-7.
40. Milani M, Pecora S; Rainbow Study Investigator Group. Clinical relevance of non-grass pollens respiratory allergies in Italy and effects of specific sublingual immunotherapy: The Rainbow Trial, a multicentre 3-year prospective observational study. Eur Ann Allergy Clin Immunol 2011; 43(4):111-6.
41. Twaroch TE, Focke M, Civaj V, Weber M, Balic N, Mari A, et al. Carrier-bound, nonallergenic Ole e 1 peptides for vaccination against olive pollen allergy. J Allergy Clin Immunol 2011; 128(1):178-84.
42. Albani M, Domenico G. The foreign population resident in Italy. Statistics in brief. Reference period: 1 January 2010 Published on: 12 October 2010. Istat - Istituto nazionale di statistica.www.istat.it.
43. Reher DS, Alcaca LS, Quinones FG, Requena M, Dominguez MIS, Gimeno AS, Stanek M. Informe Encuesta Nacional de Inmigrantes (ENI-2007). Instituto National de Estadistica. Documentos de trabajo, 2/08. www.ines.es.