percentages of $CD63^+$ basophils after stimulation with Pru p 3 preincubated with OLE were also significantly ($P = .011$) increased when compared with $CD63^+$ basophils after stimulation of Pru p 3 preincubated with STE. In addition, comparison of Pru p 3 preincubated with STE and Pru p 3 alone showed that this ligand did not have any impact on basophils' activation ($P > .05$) (Fig 2, *C*; Table E3).

In conclusion, our ligand-binding assays provided interesting results regarding the binding specificity of Pru p 3, preferably binding poly- and mono-unsaturated fatty acids as compared with saturated ones. In parallel, using an *in silico* approach, we showed conformational changes of the cavity and a shift in the tertiary structure of Pru p 3 as a consequence of OLE and OLE^- binding. Notably, the IgE ELISA performed with sera from 10 peach-allergic patients confirmed our hypothesis that exposure of the C-terminal loop due to the OLE/OLE^- binding could indeed enhance the IgE-binding activity. In contrast, binding of STE was unable to increase the IgE-binding capacity. This corroborates our idea that only those ligands that shift the tertiary structure of Pru p 3, thus exposing IgE epitopes, could increase its allergenic potential. This observation is consistent with previous studies indicating that no synthetic peptides covering areas of helix 3 or loop 3 were identified among the most reactive peptides in the SPOT analysis, probably because most of this region is mainly buried inside the compact 3-dimensional structure of Pru p 3.[7] Consistent with the data obtained by ELISA, OLE, but not STE, had a significant impact on the basophil activation. This is in line with a study on grape nsLTP where the presence of phosphatidylcholine in an *in vitro* digestion assay had not only a protective effect on the allergen but also increased the ability of the allergen to induce basophil histamine release and to elicit skin reactions in 4 patients with grape allergy.[8] It becomes clear that lipids, in addition to their role as direct immune modulators, can influence the allergenicity of proteins[9] by modifying the allergen structure and biochemical properties. Among unsaturated fatty acids, OLE is abundantly found in peach fruits, but it is also endogenously present in the lipid bilayer of the human gut. Pru p 3 seems to be presented in its holoform to the allergic individual throughout exposure and digestion. This, in turn, explains that this immunodominant B-cell epitope is conserved and surface exposed. In this context, the application of Pru p 3 in diagnostic tests should be reconsidered, using Pru p 3 together with OLE for component-resolved diagnosis to increase assay sensitivity. Furthermore, for designing low allergenic Pru p 3 variants for immunotherapy, the amino acid residues relevant for OLE interaction are the targets for mutations and thus reduce the risk of side effects during immunotherapy.

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This work was funded by the Austrian Science Fund (FWF): grant number DK W 1248-B13 to P.D. and grant number SFB F4603 to K.H.-S. Further support came from the Horizon 2020 Programme of the European Union (iNEXT grant, project no. 653706). This research was also supported in part by PL-Grid Infrastructure and by the Marie-Curie project CARAMEL within the 7th European Community Framework Programme (grant no. 626572 to R.A.).

Disclosure of potential conflict of interest: R. Aina has received grants from the Marie-Curie project CARAMEL, 7th European Community Framework Programme (grant no. 626572). B. Bohle has received grants from the Austrian Science Fund (SFB grant nos. F4610, W1212, and W1248) and the Christian Doppler Research Organization and is a board member for Allergen Online Database, Paul Ehrlich Institute, and the Christian Doppler Research Organization. The rest of the authors declare that they have no relevant conflicts of interest.

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Available online July 14, 2017.
http://dx.doi.org/10.1016/j.jaci.2017.06.016

Prevalence of primary immunodeficiencies in France is underestimated



To the Editor:

Primary immunodeficiencies (PIDs) are chronic, lifelong, inherited disorders.[1] Patients with PIDs typically require multidisciplinary care in highly specialized units at university teaching hospitals (UTHs). Prevalence is one of the most basic but key epidemiological indicator because it helps define the frequency of a condition within a population, and thus can ultimately lead to improve actions by health care providers and define more appropriate public health policies at national and international levels. On the basis of national or continental registries, the estimated minimal prevalence of PIDs varies from 1.5 to 18.8 per 100,000 inhabitants.[2,3] However, epidemiological data on PIDs are scarce and are hampered by a lack of awareness, underdiagnosis, and a lack of coordination between the different stakeholders.

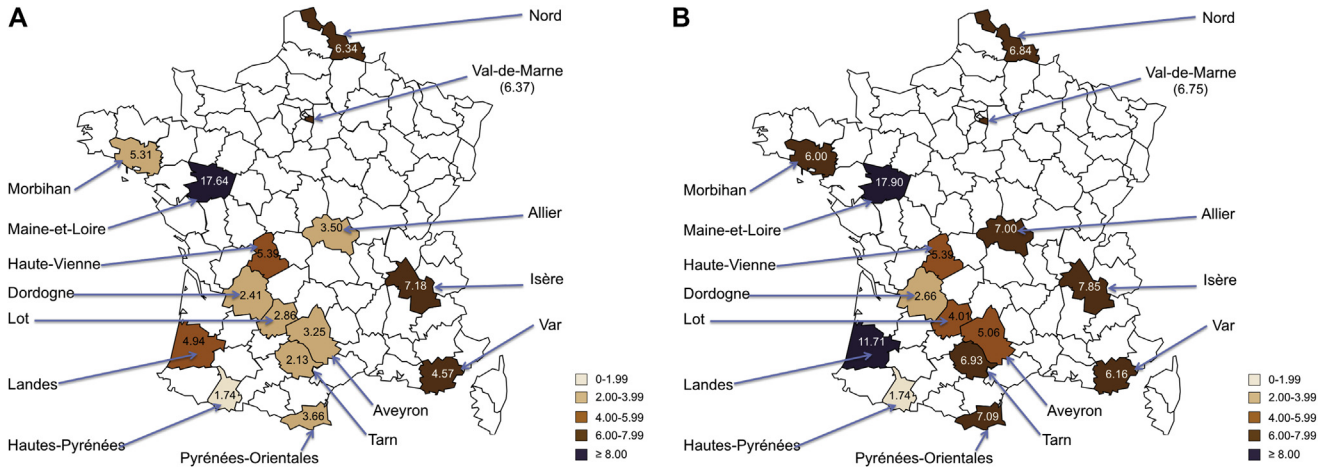


FIG 1. Prestudy and poststudy prevalence maps. **A,** A map showing the prevalence of patients with PID (per 100,000 inhabitants in each *département*) registered at UTH before the present study. **B,** A map showing the estimated prevalence of patients with PID (per 100,000 inhabitants in each *département*) after the present study.

TABLE I. Summary of the characteristics of newly identified patients

Characteristic	No. of patients	Immunoglobulin replacement therapy, no. of patients yes/no/missing data	Immunoglobulin replacement therapy (%)	Current age (y), median (Q1-Q3)
Predominantly antibody disorders	119	90/12/17	75.6	59 (47.0-72.0)
Common variable immunodeficiency	65	54/5/6	45.4	59 (47.0-72.0)
Unclassified antibody deficiencies	21	15/4/2	12.6	60 (54.0-74.0)
Isolated IgG subclass deficiency	14	8/2/4	6.7	56.5 (43.3-66.3)
Other hypogammaglobulinemias	8	3/1/4	2.5	62 (15.0-71.0)
Agammaglobulinemia	5	5/0/0	4.2	37 (34.0-42.0)
Thymoma with immunodeficiency	4	4/0/0	3.4	78 (74.8-79.5)
Dystrophia myotonica type 2 (PROMM/ZNF9)	1	1/—/—	0.8	36
Selective IgM deficiency	1	0/1/0	0	52
Innate immunity deficiencies	**5**	0/0/5		17.5 (12.3-29.5)
Chronic granulomatous disease	2	—	—	34.5 (24.3-44.8)
Defects with susceptibility to mycobacterial infection	1	—	—	21
Isolated congenital asplenia	1	—	—	7
Complement component 5 deficiency	1	—	—	29
Autoimmune and immune dysregulation syndromes	**3**	0/0/3		14 (11.5-25.0)
Autoimmune lymphoproliferative syndrome	3	—	—	—
Unclassified immunodeficiencies	**1**	1/—/—	0.8	78

Underreporting to registries is a frequent phenomenon, and thus leads to the underestimation of prevalence.[4]

By leveraging the French national PID registry, we have estimated the minimum prevalence of PIDs in France to be 4.4 per 100,000 inhabitants in 2009, with significant differences in the adjusted regional prevalences across the country.[2] In view of these epidemiological data, we sought to (1) determine putative factors linked to this heterogeneity, and (2) identify patients being treated in general hospitals or large private practices (rather than in regional PID reference centers at UTHs, which are the cornerstones of the registration process in the French PID registry). Here, we performed an epidemiologic field survey in 15 of France's 101 midlevel administrative divisions (*départements*) to screen for patients diagnosed with a PID but not having been referred to a UTH and thus not reported to the CEREDIH registry (French National Reference Center for PIDs). The *départements* were chosen as a function of (1) the local prevalence of PIDs (below, above, or at the national average), (2) whether or not a reference UTH was located within the *département*, (3) how far the *département* was from the nearest UTH, and (4) whether the *département* was mostly rural or mostly urban. The total population of these 15 *départements* is 10.6 million, which corresponds to 17% of the French population.

Before the study, the CEREDIH national registry contained data on 565 patients in these 15 *départements* (mean overall prevalence in the surveyed area was 4.38 per 100,000 inhabitants; median, 3.50; range, 1.74-13.88). A total of 480 of 567 clinical units and pharmacies replied. The response rate did not vary significantly from one area to another and distribution of no reply did not significantly differ between the areas under scrutiny. After a

careful onsite examination of medical records, the diagnosis of PID was confirmed in 219 patients. Ninety-one of the patients were being cared for by physicians in local reference centers but had not yet been entered in the CEREDIH registry. Hence, upon registration of these 91 patients, the overall prevalence of PIDs in these 15 *départements* was 5.15 (Fig 1; see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). However, the remaining 128 individuals were new patients who had not previously been referred to their local PID competence center in a UTH. The inclusion of these 128 patients increased the overall prevalence from 5.15 to 6.87 per 100,000 inhabitants (a 1.33-fold increase). The size of this increment emphasizes the value of the present methodology. Most of the newly identified patients (n = 116 [91%]) were 18 years or older and had B-cell deficiencies (109 of 128 patients [85%]) (Table I; see Tables E1 and E3 in this article's Online Repository at www.jacionline.org), which is expected because hypogammaglobulinemia is the most frequent form of PID and also corresponded to the least severe clinical presentation.

There was a strong correlation between the prestudy prevalence and the number of newly detected cases (except in 2 *départements*; see Fig E1 and Table E2 in this article's Online Repository at www.jacionline.org). There was a statistically significant difference in prevalence increment according to the mean prevalence of patients known to UTH ($P = .012$ in a Mann-Whitney U test). This result was expected, and showed that the known heterogeneity in the geographical distribution of PID was due at least in part to differences in the rate of referral to UTH. The distance between the patients' place of residence and the closest UTH was found to influence referral (Table E2; $P = .014$), because the prevalence was much higher in *départements* in which a UTH is located (n = 5) than in *départements* lacking a UTH (n = 10). The distance between the patients' place of residence and the UTH was inversely correlated with the prevalence. It is noteworthy that even though the poststudy prevalence increased most in *départements* lacking a UTH, the values were still below those for *départements* with a UTH, suggesting that other factors might have a role (such as lack of awareness on PID, lack of medical education about PID for general practitioners during their professional career, lack of access of patients to specialized medical care [due to socioeconomic status and/or geographical distances between home and these specialized centers]). No other local geographic or socioeconomic parameters had a significant influence on prevalence; these included the population density ($P = .33$), the density of physicians ($P = .33$), household income ($P = .26$), and gross domestic product ($P = .12$). The current national prevalence of PIDs in France is 8.0 per 100,000 inhabitants. On the basis of our large study, we can infer that the actual one is around 11 per 100,000, the corresponding predicted adult prevalence being around 6.7 per 100,000 inhabitants, rather than 5.5.

As expected, the identified patients tended to live in areas where the apparent prevalence was the lowest. Interestingly, the prevalence increment was strongly correlated with the distance between the patient's place of residence and the nearest UTH. Hence, distance from a UTH appears to be a barrier to the referral of adult patients. Other factors might account for these low prevalence values, which might reflect a truly lower prevalence or merely the underdiagnosis of PIDs or failure to survey all the relevant health care providers in an area.

In conclusion, our study assessed the level of underreporting and determined a corrective factor for more accurate estimation of the national prevalence of PIDs. The present study also had clinical value because the 128 newly identified patients have now been referred to a UTH and thus can receive expert care. We suggest that this type of study should be extended to the rest of France and to other countries, with a view to improving the overall management of patients with PIDs, particularly those living far from a UTH.

The European Society for Immune Deficiencies Online Registry Database was used for collecting data for this study. The cooperation of physicians and pharmacists working in the study areas was much appreciated.

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The CEREDIH received support from the French Association of Patients with Primary Immunodeficiencies (Immunodeficience primitive-Recherche-Information-Soutien; IRIS) and is funded by the French Ministry of Health. It additionally received unrestricted educational grants from LFB, GSK, CSL Behring, Shire, Octapharma, Binding Site, the Jeffrey Modell Foundation, and the patient associations AT-Europe and Trophée Guillaume.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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Available online July 18, 2017.
http://dx.doi.org/10.1016/j.jaci.2017.06.020