Childhood leukaemia and population movements in France, 1990-2003.

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Abstract

In line with the infectious hypothesis, the occurrence of cases of childhood leukaemia (CL) could be the rare consequence of common infections by one or several viral agents and isolated places subject to sudden or unusual population influxes could be at a particular risk.

The present study investigated the association between population movements and the incidence of CL, on the French national scale, over a 14-year period. Several measures based on the proportion of individuals who changed address between the last two national censuses were considered.

A positive association was found with the proportion of migrants who came from a distant place. The further the migrants came, the higher was the incidence of leukaemia, particularly among young children living in 'isolated' *communes* at the time of diagnosis (RR=1.4, 95% CI: 1.1,1.8 in the highest category of migration distance). Although the role of the population density was not so obvious, a more marked association was evidenced above a given threshold. No association with the proportion of commuters was observed.

Keywords

Childhood leukaemia; population movements; population density; infectious aetiology hypothesis

Introduction

About 20 years ago, the occurrence of a cluster of cases of childhood leukaemia (CL) in the village of Seascale (Great Britain) revived the infectious hypothesis (Kinlen, 1988). According to this hypothesis, isolated areas that experienced a large or sudden population influx are places conducive to occurrence of an epidemic of infections due to one or several common viruses. The occurrence of CL cases may then be a rare consequence of first exposures to those viral agents.

Several studies by Kinlen (Kinlen, 1988, 2006; Kinlen *et al.*, 2002; Kinlen *et al.*, 1990; Kinlen and Hudson, 1991; Kinlen and John, 1994; Kinlen *et al.*, 1993; Kinlen and Petridou, 1995) investigated the mortality associated with, or incidence of, CL in particular isolated areas that had previously been subject to large population influxes. These studies, all focusing on historically documented and specific rural population increases, showed significant relative risks, in the range 1.5-4.7, in places with the highest proportions of incomers, compared to the reference group. Similarly, population mixing, induced by the arrival of men construction workers, was found positively associated with the incidence of childhood lymphoblastic leukaemia in French rural 'communes' located close to two nuclear sites (Boutou *et al.*, 2002).

Elsewhere, population mixing has mainly been defined as the proportion of residents who changed address over a particular time period, or in the year before a census (Dickinson *et al.*, 2002; Labar *et al.*, 2004; Nyari *et al.*, 2003; Nyari *et al.*, 2006; Parslow *et al.*, 2002; Rudant *et al.*, 2006; Stiller and Boyle, 1996) or as the percentage change in population size (Koushik *et al.*, 2001; Langford, 1991). Overall, the studies seem in favour of a positive association between the incidence of, or mortality associated with, CL and the proportions of migrants, even though a few authors reported a negative association (Law *et al.*, 2003; Parslow *et al.*, 2002).

A few studies also evidenced that the further the migrants came the higher was the incidence of CL (Dickinson *et al.*, 2002; Rudant *et al.*, 2006; Stiller and Boyle, 1996).

In a recent French cohort (Rudant *et al.*, 2006), a positive association between population mixing and the incidence of childhood acute lymphoblastic leukaemia (ALL) was evidenced, particularly for children living in isolated areas with a population density greater than a given threshold at the time of birth.

The present study aimed at investigating further on a national scale the role played by population movements in the incidence of CL over a 14-year period. The places of residence at the time of diagnosis were considered with a focus on their isolation status.

Material and methods

In 1999, mainland France consisted of 36,565 *communes*, the smallest administrative unit, 95 *départements* and 22 *régions*. Due to the merging or splitting of several *communes* before 1999, information was sometimes available only for merged *communes*. The whole of the country was finally divided into 36,347 *communes* or combinations of *communes* that, for simplicity's sake, have still been referred to as *communes*.

Study design

This ecological study was conducted on the national scale in France. All cases of CL registered in the French National Registry of Childhood Haematopoietic malignancies (RNHE, 1990) and diagnosed between 1990 and 2003 were included.

Each case was associated with its *commune* of residence at the time of diagnosis.

Characteristics of the communes

In order to define the status of each *commune* at the beginning of the study period (in 1990) two classifications provided by the French National Institute for Statistics and Economic Studies (INSEE) were considered, the Urban Zoning Classification and the Urban Unit classification (both further described in (Rudant *et al.*, 2006)).

The Urban Zoning Classification, based on influence and dependence in terms of employment, permitted to identify 'attracting' *communes* that offered a substantial number of jobs and thus attracted commuters living in other *communes*. On the basis of this classification, "dependent" *communes* were then defined as *communes* with at least 40% of their economically active population working outside, in one or several other urban 'attracting' *communes*. Overall, 'attracting' *communes* and dependent *communes* accounted for about 9% and 29% of *communes*, respectively.

The Urban Unit classification classified the French *communes* by the population size of the Urban Unit to which they belonged. An Urban Unit was defined as a group of *communes* in which the distance between dwellings was not more than 200 metres.

Based on those criteria, in this study a *commune* was then considered *a priori* 'isolated' if it belonged to an Urban Unit with a population of less than 5000 inhabitants

or to a rural *commune*, and was neither an 'attracting' *commune* nor a 'dependent' *commune* in 1990. A few *communes* called "urban" by INSEE were therefore included in the 'isolated' *commune* group, but they are small, not 'attracting', not 'dependent' and situated in remote areas. The 'isolated' *communes* accounted for 61% of *communes* and 18.5% of French population in 1990.

Measures of population mixing

The population movements between the last two national population censuses were used as proxy measures of population mixing.

The number of individuals who moved from a *commune* to another between 1990 and 1999 was the initial focus. In order to take account of the distance covered by the migrants, the numbers of people living in a *commune* located outside the *département*, outside the *région* or in a distant *commune* in 1990 were then considered. The distance threshold above which a *commune* was considered distant from another was defined *a priori* as the median distance covered by the migrants between 1990 and 1999, 100 km overall, 60 km for 'isolated' *communes* and 120 km for 'non-isolated' *commune*. All these measures of population movement were then considered as proportions of the 1999 population.

We also considered the weighted average migration distance d_i defined by $\overline{d_i} = \frac{1}{m_i}\sum_k \left(m_{k,i} * d_{k,i}\right)$, in which $m_{k,i}$ is the number of migrants who moved from a *commune* k to given *commune* i, $m_i$the total number of immigrants in *commune* i and $d_{k,i}$ the distance between the *communes* i and k. This measure was introduced in regression models with adjustment for the overall proportion of migrants. Lastly, the proportion of regular commuters was evaluated for each *commune*, from the 1999 census data, as the sum of the economically active people living in a given *commune* but working outside it and those living outside it but working in it, divided by the 1999 population of the *commune*.

Statistical analyses

Population estimates

The INSEE provided population estimates on the *commune* scale for the two census years 1990 and 1999, and population estimates on the *département* scale from 1990 to 2003 (a French *département* consists of about 385 *communes* on average).

The populations between the two censuses and after the year 1999, on the *commune* scale, were then estimated as follows:

$$\hat{pop}_{i,j} = \frac{\hat{pop}_{i,1999}}{\hat{pop}_{dep(i),1999}} * \hat{pop}_{dep(i),j}$$

In which i and j the index-numbers for a given *commune* and a given year, respectively, $\hat{pop}_{i,j}$ is the population estimate for the *commune* i in year j and $\hat{pop}_{dep(i),j}$ is the population estimate for the *département* containing the *commune* i and for the year j (source INSEE).

Expected number of cases of CL

The numbers of cases of CL expected in each French *commune* over the study period 1990-2003 were based on the population estimates and the national 5-year age–specific incidence rates provided by the RNHE.

Regression models

The associations between the various measures of population movements and the incidence of CL in France were investigated using Poisson regression models.

Each variable was incorporated in the statistical models as a three-category variable, the breakpoints being chosen *a priori* on the basis of the quintile distribution of the expected numbers of cases, in order to isolate the highest quintile of exposure. The first two groups were then defined so that they each included 40% of the total number of expected cases. The Poisson regression models enabled estimation the SIRR as the ratio between the SIR (standardized incidence ratio) estimated for a category and the SIR of the baseline category. Cutpoints were defined separately for all *communes*, 'isolated' *communes* and 'non-isolated' *communes*. However, when the variables varied only

slightly with isolation status, in terms of distribution of the expected cases, common cutpoints for the various groups of *communes* were adopted.

Additional analyses were conducted with stratification by age groups (0-4 years, 5-9 years and 10-14 years), isolation status of the *communes* ('isolated' *communes*, 'non-isolated' *communes*) and population density. The latter was transformed into a three-category variable so that each group contained the same number of 0-14 year-old expected cases. However, the group of 'isolated' *communes* was only split at the median because of the lower number of expected cases. The breakpoints were then 180 and 1729 inhabitants per square kilometre (inh/km²) in the overall analyses, 394 and 2607 inh/km² for the group of 'non-isolated' *communes* and 45 inhab/km² in the group of 'isolated' *communes*. The analyses of weighted average distance of migration were systematically adjusted for the total proportion of migrants.

Lastly, some analyses were performed for common B-cell lymphoblastic leukaemia (common B-cell ALL).

All the analyses were performed with the SAS® and R software.

Results

Demographic characteristics of the communes

In the present study, mainland France was divided into 36,347 *communes*, 22,252 of which were 'isolated' (60%). These 'isolated' *communes* were inhabited by only 18.5% of the total French population which reached 56.6 million in 1990 (58.5 million in 1999), with about 20% aged up to 14 years. France is highly heterogeneous with *commune* populations ranging from 1 to more than 2,000,000 inhabitants with median and mean populations of about 350 and 1,500 inhabitants, respectively. Similarly, the distribution of the population density was highly heterogeneous (from 1 to more than 22,000 inh/km² with a median of 33). As expected, the 'isolated' *communes* were characterized by a smaller population and a lower population density.

Population movements

Overall, 19,657,175 people changed address between the two censuses, 18,336,140 of whom came from a *commune* in mainland France for which the isolation status was

available. About 18% of the migrants moved to an 'isolated' *commune*. The median distance covered by all the migrants was about 100 km and was 60 km and 120 km for 'isolated' *communes* and 'non-isolated' *communes* of destination, respectively (Table 1). Overall, half of the *communes* were subject to a total population influx of between 26% and 38% of their 1999 population (Table 1). 'Non-isolated' *communes* had a slightly greater proportion of migrants than 'isolated' *communes*. The median proportions of migrants who came from another *département* and from another *région* were equal to 11.4% and 7.8%, respectively. Slightly higher proportions were observed in 'isolated' *communes* than in 'non-isolated' *communes*. The proportions of migrants who lived in a distant *commune* in 1990 were mainly less than 10% and were slightly higher in the 'isolated' *communes*. The 'isolated' *communes* also tended to be associated with a higher weighted average migration distance than the 'non-isolated' *communes* (Table 1).

Lastly, half of the *communes* had between 30.5% and 45% regular commuters, and the proportions appeared markedly greater in the 'non-isolated' *commune* group.

Distribution of the cases of childhood leukaemia (CL) over 1990-2003

In all, 6288 children aged 0-14 years were included in the National Registry of Childhood Haematopoietic malignancies with a diagnosis of leukaemia between 1990 and 2003. The *commune* of residence at the time of diagnosis was missing for 14 children (0.2%). Finally, 6274 cases of CL were included in the analyses, half of the cases were aged less than 5 years at the time of diagnosis. A total of 4090 cases of childhood common B-cell ALL were registered over 1990-2003 and accounted for 65% of all the cases.

Overall, 5220 cases of CL (83% of the total) were diagnosed in a 'non-isolated' *commune*.

Incidence of CL over the period 1990-2003 and population movements in the French communes between 1990 and 1999

Overall, no association with the total proportion of migrants, proportion of migrants from another *département* or proportion of commuters was evidenced (Table 2). However, an increased incidence was observed with the proportion of migrants who came from another *région*, particularly in the 'isolated' *commune* group. A proportion of migrants greater than 13% was thus associated with a significant 18% increase in the incidence of CL.

Similarly, a slight increase in incidence was evidenced in the group with the highest proportions of migrants from distant *communes* (SIRR=1.08 [1.02;1.16]). This increase was observed in both isolation groups, with a greater magnitude in the 'isolated' *communes* although the association was of borderline statistical significance (SIRR=1.14 [0.97;1.33]).

Adjusting for the total proportion of incomers, the weighted average migration distance was slightly associated with the incidence of CL. This positive association was, however, more marked for the 'isolated' *communes* (SIRR= 1.17 [1.02;1.34] for a distance in the range 82-185 km and 1.24 [1.02;1.5] for a distance greater than 185 km)

Overall, most of the above results were found, mostly reinforced, in children aged less than 5 years (Table 3). The proportion of migrants from another *région* was associated with a 20% increase in the incidence of CL for the highest proportions. In the 'isolated' *commune* group, a proportion of migrants from a distant *commune* greater than 12% was associated with a 25% increase in the incidence of CL (SIRR=1.25 [1.01;1.56]). Similarly, allowing for the total proportion of migrants, the 'isolated' *communes* with a weighted average migration distance of more than 185 kilometres were at a significant increased risk of CL (SIRR=1.41 [1.09;1.83]). Some of the associations were still observed in the 5-9 year age group, but none remained for children aged more than 10 years (results not shown)

When stratifying by the population density, no association with the total proportion of migrants was evidenced (results not shown). However, a non-significant increase

appeared in the 'isolated' *communes* with a population density of less than 45 inh/km² (SIRR=1.28 [0.91;1.79] for proportions of migrants greater than 38%).

Considering all *communes*, whatever the proxy measure of population mixing based on the migration distance – proportion of migrants from another *région*, from a distant *commune* or the weighted average migration distance – the positive association with the incidence of CL among 0-4 year-old children seemed to be restricted to the *communes* with low population density (≤180 inhab/km² - table 4). In those *communes*, the various measures of population movements showed a more than 20% increase in incidence associated with the highest category (SIRR=1.27 [1.07;1.51] for the proportion of migrants from another *région*, SIRR=1.22 [1.03;1.45] for the proportion from a distant *commune* and SIRR=1.28 [1.04;1.58] for the weighted average migration distance).

In the 'isolated' *commune* group, the influence of population density was less clear-cut. However, a striking association with the weighted average migration distance was observed in *communes* with a population density greater than > 45 inhab/km² (SIRR=1.25 [0.97;1.61] and SIRR=1.72 [1.23;2.39] for a distance between 82 and 185 km and greater than 185 km, respectively).

The results observed in the 'non-isolated' *commune* group were quite similar to those observed overall, even though they were only on the borderline of statistical significance and of a slightly smaller magnitude.

When the analyses were restricted to common B-cell ALL in children aged up to 14 years the results were quite similar but the role of the population density in 'isolated' *communes* became less clear (not shown).

Although there were slight inconsistencies, the results of the analyses conducted on the two sub-periods, 1990-1996 and 1997-2003, were in favour of a positive association between the incidence of CL and population movements.

Using linear interpolation between the two censuses to estimate the populations on the *commune* scale between 1990 and 1999 and over 1999 did not change the results. Similarly, the results remained stable when the *communes* that merged or split (about 200 *communes*) were excluded.

Discussion

On the national scale, the incidence of leukaemia was found to be associated with the population movements among children living in 'isolated' *communes* at the time of diagnosis, with a more marked association above a given threshold of population density. Although of smaller magnitude, similar associations were evidenced among children who lived in 'non-isolated' *communes* that were less densely populated. The associations were also more pronounced in the 0-4 year age group, but were not specific to common B-cell ALL. The analyses conducted on the two sub-periods led to similar conclusions, with however more marked associations over 1997-2003. Sensitivity analyses showed the stability of the results with respect to the population estimates on the *commune* scale and the changes in *communes* over time.

The present study addressed the data generated by 14 years of national registration of leukaemia, with an exhaustiveness estimated to be 99.2% (Clavel *et al.*, 2004). The number of missing data was so small (0.2%) that they are unlikely to have played a major role in the results. It also benefited from INSEE's ability to provide up-to-date descriptions of France in terms of urban status, and characterize between-census population movements. Although there is a 10-year delay between the censuses, which is a large time scale to account for recent and rapid changes in *communes* and may have introduced misclassifications, there is no obvious reason why those misclassifications would be differential and related to migration distance. In particular, our measure of population movements would not have been able to detect any temporary population movement that had occurred between the censuses (eg wartime evacuation). Besides, a change in the population movement patterns may be more important, under the population mixing hypothesis, than a sustained high proportion of migrants. The measures of population movements considered in the present study, mostly based on changes in address between 1990 and 1999, provided no indication of whether a high level of migrants was new. Areas that had been associated with a substantial proportion of migrants at some time before 1990 were considered together with areas where the arrival of migrants was new although they may be not strongly expected to show an excess following the arrival of other migrants between 1990 and 1999.

With regard to the infectious hypothesis, population movements may have a greater impact when they occur around the time of birth. Using the place of residence at the time of diagnosis may be less accurate and could be one of the reasons why the associations described above seemed weaker than those reported by Rudant *et al.* (Rudant *et al.*, 2006).

Proportion of migrants and migration distance

Some authors investigated the role played by population movements in the occurrence of cases of CL in localised isolated areas that had been subject to extreme and unusual population influxes (Boutou *et al.*, 2002; Dickinson and Parker, 1999; Kinlen, 1988, 2006; Kinlen *et al.*, 2002; Kinlen *et al.*, 1990; Kinlen and Hudson, 1991; Kinlen and John, 1994; Kinlen *et al.*, 1993; Kinlen and Petridou, 1995). Those studies, based on specific rural population increases, were mainly concordant in their finding of an increased risk of CL with an increasing proportion of incomers.

Unlike those studies that focused on new population increases, the present study considered the migrants who moved from a *commune* to another between the last two censuses with no account of whether the high levels of migration were new. Besides, the population variations between the census years were so skewed on the *commune* scale that this measure could not be considered in the present study.

Several other studies have shown that areas with high proportions of migrants or marked changes in population were at a significantly higher risk of CL than other areas (Alexander *et al.*, 1997; Dickinson *et al.*, 2002; Koushik *et al.*, 2001; Labar *et al.*, 2004; Langford, 1991; Nyari *et al.*, 2006; Rudant *et al.*, 2006; Stiller and Boyle, 1996; Wartenberg *et al.*, 2004). A positive association was observed in Ontario for children less than 5 years old living in rural areas, in contrast to a slight negative association in urban areas (Koushik *et al.*, 2001), while in UK Dickinson *et al.* evidenced an increased risk of disease only in urban census wards. Two other studies, involving a substantial number of cases, did not demonstrate any significant association with the overall proportion of people who changed address in the year before a census, but evidenced

instead a negative association with a index of mixing diversity (Law *et al.*, 2003; Parslow *et al.*, 2002).

In the present study, where the role of population movements was investigated in 'isolated' and 'non-isolated' *communes*, a positive non-significant association was evidenced only for the subgroup of *communes* that were 'isolated' and had a low population density. The distribution of the proportions of migrants was highly skewed, with an inter-quartile distance of about 10%, which could have hampered detection of a potential association. Moreover, considering the overall proportion of individuals who moved from a *commune* to another, regardless of the distance, was maybe an inaccurate measure of migrations as it included all movements without any restriction.

Only three studies investigated the role played by the migration distance in the incidence of CL, either directly, by taking into account the average distance between destination and the initial areas (Stiller and Boyle, 1996) or by considering the proportions of migrants from distant areas (other district, other region, outside the country) (Dickinson *et al.*, 2002; Rudant *et al.*, 2006). All the studies found a positive association with the migration distance.

In the present study, the distance covered by the migrants was considered by using three different measures that were significantly correlated. The further the migrants came the higher was the incidence of CL, particularly among children aged 0-4 years and living in 'isolated' areas at the time of diagnosis. These results were in line with the literature and somewhat concordant with the infectious hypothesis put forward by Kinlen, insofar as children who lived in 'isolated' *communes* subject to population influx seemed to be at a higher risk of leukaemia. The involvement of migration distance may be explained by the fact that the further the migrants travelled the less likely they were to have had much previous contact with the local population and to share the same immune status with respect to the hypothetical viral agent.

Population density

The associations were evidenced in both isolation status groups but only in *communes* with a population density of less than 394 inhabitants per square kilometre for the 'non-isolated' *commune* group. This may stem from possible inaccuracy in the definition of the isolation status. The *communes* that were located in the vicinity of an urban pole, and thus dependent on it for employment, were considered 'non-isolated', regardless of their population size or population density. It was considered, perhaps erroneously, that the people who lived in those *communes* were likely to share a common immunity with the people who lived in the urban pole. If the association between the incidence of CL and the migration distance were restricted to isolated locations, as proposed by Kinlen, the results found in the 'non-isolated' *communes* could reflect misclassification with respect to the real isolation status of the *communes*.

The involvement of population density may also indicate that the evaluation of the isolation status of French *communes*, which was intended to identify communities with low background immunization, may not have been sufficiently pertinent to the infectious hypothesis.

However, a striking increase in the incidence of CL was found with the weighted average migration distance in the 'isolated' *commune* group, but only in *communes* with a population density greater than 45 inhabitants per square kilometre. This result, in line with the results of the birth cohort study recently carried out in France (Rudant *et al.*, 2006), seems to be in favour of a real role of population density. There may be a threshold below which the suspected infection cannot spread because of the limited number of person-to-person contacts.

Commuting

No association with the proportion of commuters residing in the French *communes* was evidenced in the present study. The results were concordant with the results published by Stiller (Stiller and Boyle, 1996), even if the latter used a slightly different definition of commuting to that used herein. Kinlen also investigated the role of commuting in the incidence of CL and observed a 80% increase in locations with highest changes in the proportion of commuters (Kinlen *et al.*, 1991). Regarding the

infectious hypothesis, a change in commuting patterns over time may be more important than a sustained high level.

Conclusion

The high quality of the data provided by INSEE and the French National Registry of childhood haematopoietic malignancies enabled investigation of the association between the incidence of CL over a 14-year period and population movements. In contrast to Kinlen's work, which was based on specific rural population movements, the present study was based on migration measures estimated over a 10-year period on a national scale, and accounted for both the isolation status and population density of the *communes*.

The incidence of CL was associated with population movements for young children living in 'isolated' areas at the time of diagnosis. This finding was consistent with the possible involvement of viral agents in the occurrence of cases of leukaemia. Although the associations seemed more marked above a given threshold, the role played by population density remains unclear and further research is necessary.

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Table 1 - Distribution of the migration distance and distribution of the proxy measures of population mixing, for all *communes* and by the 'isolation' status (see text) of the *communes* (max: maximum; min: minimum; Q1: first quartile; Q3: third quartile).

	Mean	Min.	Q1	Median	Q3	Max.
Migration distance						
All *communes*	196.6	0.0	25.3	95.4	328.4	1,897.9
'isolated' *communes*	160.7	0.0	17.8	58.2	247.0	1,370.1
'non-isolated' *communes*	212.2	0.0	30.2	117.5	357.0	1,897.9
Proxy measures of population mixing						
Proportion of migrants (%)						
All *communes*	31.9	0.0	26.3	31.9	37.5	100.0
'isolated' *communes*	30.5	0.0	24.7	30.2	36.0	100.0
'non-isolated' *communes*	34.3	0.0	29.1	34.1	39.2	79.4
Proportion of migrants from another *département* (%)						
All *communes*	12.7	0.0	7.3	11.4	16.6	64.1
'isolated' *communes*	13.2	0.0	7.9	12.1	17.2	64.1
'non-isolated' *communes*	11.8	0.0	6.6	10.3	15.4	59.4
Proportion of migrants from another *région* (%)						
All *communes*	9.1	0.0	4.8	7.8	11.9	63.4
'isolated' *communes*	9.8	0.0	5.3	8.7	13.0	63.4
'non-isolated' *communes*	8.0	0.0	4.2	6.8	10.1	58.6
Proportion of migrants from distant [(1)] *communes* (%)						
All *communes*	7.6	0.0	3.8	6.5	10.3	62.5
'isolated' *communes*	8.3	0.0	4.1	7.3	11.3	62.5
'non-isolated' *communes*	6.5	0.0	3.5	5.6	8.7	58.6
Weighted average migration distance (km)						
All *communes*	98.6	1.6	54.4	81.1	126.7	1269.7
'isolated' *communes*	109.7	1.6	60.1	93.0	144.1	898.8
'non-isolated' *communes*	80.9	2.4	48.7	68.1	97.8	1269.7
Proportion of commuters (%)						
All *communes*	39.9	0.0	30.5	37.7	45.1	2664.0
'isolated' *communes*	34.8	0.0	27.1	33.1	39.5	1393.8
'non-isolated' *communes*	47.9	12.9	38.8	44.0	50.7	2663.6

1: ≥100 km for all *communes;* ≥60 km for 'isolated' *communes* and ≥120 km for 'non-isolated' *communes*.

Table 2 - Incidence of CL over the period 1990-2003 in children aged 0-14 years and population movements in the French *communes* between 1990 and 1999, for all destination *communes* and by the 'isolation' status (see text) of the *communes* (E: expected number of cases; SIRR: SIR (Standardized incidence ratio) ratio). SIRR estimated by Poisson regression.

		All *communes*			**'Isolated' *communes***			**'Non-isolated' *communes***		
		E	**SIR R**	CI95	E	**SIR R**	CI95	E	**SIR R**	CI95
All migrants	≤30%	2584.9	**1**	Ref.	491.6	**1**	Ref.	2092.2	**1**	Ref.
	≤38%	2483.9	**1.05**	[0.99-1.11]	408.3	**1.06**	[0.93-1.21]	2075.6	**1.04**	[0.98-1.11]
	>38%	1205.4	**0.98**	[0.92-1.05]	167.8	**1.05**	[0.88-1.25]	1037.6	**0.97**	[0.9-1.04]
Migrants from another *département*	≤12%	2424.8	**1**	Ref.	511.2	**1**	Ref.	1912.6	**1**	Ref.
	≤21%	2554.4	**1.01**	[0.96-1.07]	432.2	**1.03**	[0.9-1.17]	2122.2	**1.00**	[0.94-1.07]
	>21%	1294.9	**0.99**	[0.93-1.06]	124.3	**1.06**	[0.87-1.29]	1170.5	**0.98**	[0.91-1.06]
Migrants from another *région*	≤7%	2407.8	**1**	Ref.	367.8	**1**	Ref.	2039.0	**1**	Ref.
	≤13%	2731.4	**1.01**	[0.96-1.07]	453.7	**1.09**	[0.95-1.26]	2277.8	**1**	[0.94-1.06]
	>13%	1134.8	**1.08**	[1.01-1.16]	246.2	**1.18**	[1.01-1.39]	888.6	**1.06**	[0.98-1.15]
Migrants from distant(1) *communes*	≤L1(2)	2765.1	**1**	Ref.	388.7	**1**	Ref.	2079.8	**1**	Ref.
	≤L2(3)	2237.8	**1.06**	[1-1.12]	447.4	**1.02**	[0.89-1.18]	2023.3	**1.02**	[0.96-1.09]
	>L2(3)	1271.2	**1.08**	[1.02-1.16]	231.6	**1.14**	[0.97-1.33]	1102.2	**1.08**	[1-1.16]
Weighted average migration distance (4)(km)	≤82	2507.7	**1**	Ref.	421.3	**1**	Ref.	2085.4	**1**	Ref.
	≤185	2775.6	**1.05**	[1-1.11]	513.3	**1.17**	[1.02-1.34]	2262.2	**1.03**	[0.97-1.09]
	>185	990.8	**1.10**	[1.02-1.18]	133.1	**1.24**	[1.02-1.5]	857.7	**1.07**	[0.99-1.16]
Commuters	≤L3(5)	2424.1	**1**	Ref.	405.7	**1**	Ref.	2124.5	**1**	Ref.
	≤L4(6)	2559.9	**1.03**	[0.97-1.09]	442.1	**1.13**	[0.98-1.29]	1949.1	**0.96**	[0.9-1.02]
	>L4(6)	1260.0	**1.01**	[0.94-1.08]	219.8	**1.10**	[0.93-1.3]	1131.7	**0.98**	[0.91-1.05]

1: ≥100 km for all *communes;* ≥60 km for 'isolated' *communes* and ≥120 km for 'non-isolated' *communes*
2: 0.07 for all *communes*; 0.08 for 'isolated' *communes*; 0.06 for 'non-isolated' *communes*
3: 0.12 for all *communes*; 0.14 for 'isolated' *communes*; 0.11 for 'non-isolated' *communes*.
4: adjusted for the proportion of migrants.
5: 0.42 for all *communes*; 0.33 for 'isolated' *communes*; 0,45 for 'non-isolated' *communes*
6: 0.59 for all *communes*; 0.44 for 'isolated' *communes*; 0,60 for 'non-isolated' *communes*.

Table 3 - Incidence of CL over the period 1990-2003 in children aged 0-4 years and population movements in the French *communes* between 1990 and 1999, for all destination *communes* and by the 'isolation' status (see text) of the *communes* (E: expected number of cases; SIRR: SIR (Standardized incidence ratio) ratio). SIRR estimated by Poisson regression.

		All *communes*			**'Isolated' *communes***			**'Non-isolated' *communes***		
		E	**SIRR**	CI95	E	**SIRR**	CI95	E	**SIRR**	CI95
All migrants	≤30%	1293.5	**1**	Ref.	233.5	**1**	Ref.	1059.5	**1**	Ref.
	≤38%	1237.4	**1.05**	[0.97-1.13]	199.5	**1.06**	[0.88-1.28]	1037.9	**1.04**	[0.96-1.13]
	>38%	599.3	**1.02**	[0.92-1.12]	83.1	**1.15**	[0.9-1.46]	516.2	**0.99**	[0.89-1.11]
Migrants from another *département*	≤12%	1171.3	**1**	Ref.	245.4	**1**	Ref.	925.4	**1**	Ref.
	≤21%	1277.6	**0.98**	[0.91-1.06]	210.3	**0.99**	[0.83-1.19]	1067.3	**0.98**	[0.9-1.07]
	>21%	681.3	**0.97**	[0.88-1.06]	60.5	**1.09**	[0.84-1.43]	620.8	**0.95**	[0.86-1.06]
Migrants from another *région*	≤7%	1177.9	**1**	Ref.	176.2	**1**	Ref.	1001.2	**1**	Ref.
	≤13%	1380.8	**1.00**	[0.93-1.09]	220.3	**1.07**	[0.88-1.31]	1160.5	**0.99**	[0.91-1.08]
	>13%	571.5	**1.09**	[0.99-1.21]	119.7	**1.20**	[0.95-1.5]	451.8	**1.07**	[0.96-1.19]
Migrants from distant[1] *communes*	≤L1[2]	1353.5	**1**	Ref.	186.4	**1**	Ref.	1021.3	**1**	Ref.
	≤L2[3]	1132.0	**1.05**	[0.97-1.13]	217.7	**0.95**	[0.78-1.15]	1029.9	**1.02**	[0.94-1.12]
	>L2[3]	644.7	**1.11**	[1.02-1.22]	112.2	**1.25**	[1.01-1.56]	562.3	**1.09**	[0.98-1.21]
Weighted average migration distance [4](km)	≤82	1223.1	**1**	Ref.	203.8	**1**	Ref.	1018.8	**1**	Ref.
	≤185	1397.1	**1.06**	[0.98-1.14]	248.5	**1.19**	[0.99-1.44]	1148.6	**1.03**	[0.95-1.12]
	>185	510.0	**1.14**	[1.03-1.26]	63.9	**1.41**	[1.09-1.83]	446.1	**1.09**	[0.98-1.22]
Commuters	≤L3[5]	1208.9	**1**	Ref.	194.3	**1**	Ref.	1053.9	**1**	Ref.
	≤L4[6]	1270.5	**0.98**	[0.91-1.06]	214.4	**1.12**	[0.93-1.36]	973.5	**0.9**	[0.82-0.98]
	>L4[6]	650.8	**0.96**	[0.87-1.05]	107.5	**1.17**	[0.93-1.48]	586.1	**0.93**	[0.84-1.03]

1: ≥100 km for all *communes;* ≥60 km for 'isolated' *communes* and ≥120 km for 'non-isolated' *communes*
2: 0.07 for all *communes*; 0.08 for 'isolated' *communes*; 0.06 for 'non-isolated' *communes*
3: 0.12 for all *communes*; 0.14 for 'isolated' *communes*; 0.11 for 'non-isolated' *communes*.
4: adjusted for the proportion of migrants.
5: 0.42 for all *communes*; 0.33 for 'isolated' *communes*; 0,45 for 'non-isolated' *communes*
6: 0.59 for all *communes*; 0.44 for 'isolated' *communes*; 0,60 for 'non-isolated' *communes*.

Table 4 - Incidence of CL over the period 1990-2003 in children aged 0-4 years and population movements between 1990 and 1999 with stratification by the 1990 population density of the French *communes*.

		Low density			Medium density			High density		
		E	**SIRR**	CI95	E	**SIRR**	CI95	E	**SIRR**	CI95
All *communes*		≤180 inh/km²			180-1729 inh/km²			>1729 inh/km²		
Migrants from another région	≤ 7%	382.3	**1.00**	Ref.	367.4	**1.00**	Ref.	427.7	**1.00**	Ref.
	≤ 13%	421.3	**1.10**	[0.95-1.27]	422.0	**0.96**	[0.84-1.10]	537.5	**0.96**	[0.85-1.10]
	> 13%	190.9	**1.27**	[1.07-1.51]	215.1	**1.01**	[0.86-1.19]	165.5	**1.01**	[0.84-1.21]
Migrants from a distant commune (> 100 km)	≤ 7%	480.7	**1.00**	Ref.	433.0	**1.00**	Ref.	439.3	**1.00**	Ref.
	≤ 12%	340.7	**1.06**	[0.92-1.22]	345.3	**1.09**	[0.95-1.26]	446.0	**0.99**	[0.87-1.14]
	> 12%	173.1	**1.22**	[1.03-1.45]	226.2	**1.04**	[0.89-1.22]	245.4	**1.09**	[0.94-1.28]
Weighted average migration distance (km)	≤ 82	454.9	**1.00**	Ref.	404.4	**1.00**	Ref.	363.4	**1.00**	Ref.
	≤185	438.4	**1.12**	[0.98-1.28]	457.9	**1.06**	[0.93-1.21]	500.8	**1.00**	[0.87-1.14]
	>185	101.2	**1.28**	[1.04-1.58]	142.3	**1.09**	[0.91-1.31]	266.5	**1.09**	[0.91-1.25]
'Non-isolated' *communes*		≤394 inh/km²			394- 2607 inh/km²			>2607 inh/km²		
Migrants from another région	≤ 7%	323.0	**1.00**	Ref.	335.1	**1.00**	Ref.	343.0	**1.00**	Ref.
	≤ 13%	345.6	**1.02**	[0.87-1.19]	348.8	**0.97**	[0.84-1.12]	466.1	**1.00**	[0.86-1.15]
	> 13%	149.2	**1.19**	[0.99-1.44]	166.3	**0.96**	[0.80-1.15]	136.4	**1.08**	[0.88-1.31]
Migrants from a distant commune (> 120 km)	≤ 7%	353.3	**1.00**	Ref.	355.4	**1.00**	Ref.	312.6	**1.00**	Ref.
	≤ 12%	302.1	**1.04**	[0.89-1.21]	306.7	**1.03**	[0.88-1.19]	421.1	**1.02**	[0.88-1.19]
	> 12%	162.4	**1.19**	[0.99-1.43]	188.1	**0.99**	[0.83-1.18]	211.7	**1.11**	[0.93-1.32]
Weighted average migration distance (km)	≤ 82	388.6	**1.00**	Ref.	332.8	**1.00**	Ref.	297.5	**1.00**	Ref.
	≤185	338.2	**1.06**	[0.92-1.23]	408.9	**1.02**	[0.88-1.18]	401.5	**1.02**	[0.87-1.19]
	>185	91.1	**1.21**	[0.98-1.51]	108.6	**0.98**	[0.79-1.21]	246.4	**1.10**	[0.93-1.3]
'Isolated' *communes*		≤45 inh/km²			>45 inh/km²					
Migrants from another région	≤ 7%	83.8	**1.00**	Ref.	92.4	**1.00**	Ref.			
	≤ 13%	110.5	**1.04**	[0.76-1.41]	109.8	**1.11**	[0.86-1.44]			
	> 13%	66.4	**1.27**	[0.91-1.77]	53.3	**1.17**	[0.86-1.60]			
Migrants from a distant commune (> 60 km)	≤ 8%	88.6	**1.00**	Ref.	97.8	**1.00**	Ref.			
	≤ 14%	109.2	**0.95**	[0.7-1.29]	108.5	**0.95**	[0.73-1.24]			
	> 14%	62.9	**1.21**	[0.87-1.68]	49.3	**1.35**	[1.00-1.81]			
Weighted average migration distance (km)	≤ 82	99.7	**1.00**	Ref.	104.1	**1.00**	Ref.			
	≤ 185	129.2	**1.14**	[0.86-1.50]	119.3	**1.25**	[0.97-1.61]			
	> 185	31.8	**1.09**	[0.71-1.66]	32.1	**1.72**	[1.23-2.39]			

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