A Childhood Leukaemia Cluster in Milan: Possible Role of Pandemic AH1N1 Swine Flu Virus

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Outline of presentation

- Aetiology of leukaemia
- Leukaemia cluster in Milan
- Screening of risk factors
- Possible role of AH1N1

Infections and childhood ALL: epidemiological hypotheses

Delayed-infection hypothesis

common but delayed infections promote the second hit that leads to overt leukaemia

Greaves (1988, 2006)

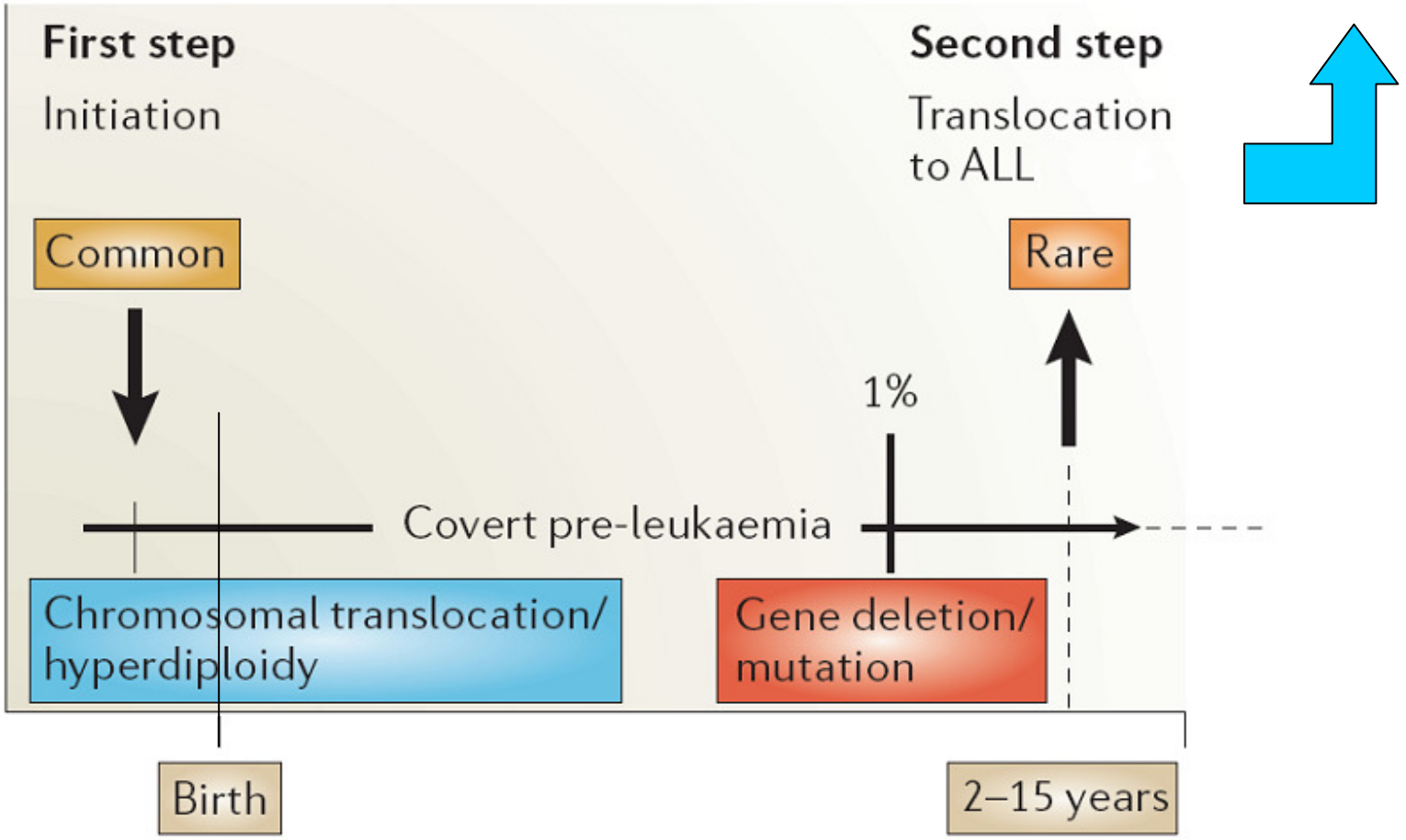
Population mixing hypothesis

an excess of childhood leukaemia would be seen in locations that had an unusual type of population mixing.

Kinlen (1988, 1995, 2011)

The natural history of childhood ALL

Only ~ 1% of that 1% have a second or more genetic hits to create an overt leukaemia.



Geographical incidence of childhood ALL

Higher rates were observed in more resource-rich countries and among more affluent populations within countries, while lower rates are observed in resource-limited countries and more deprived populations within countries.

Table 1
Incidence of childhood leukaemia – international comparisons[a] (age standardised rates per million).

Registry	Leukaemia	ALL	Lymphomas
Denmark (1983–1991)	53	42.8	11.8
Australia (1982–1991)	49.9	39.9	13.3
Sweden (1983–1989)	48.7	40.1	12.9
USA SEER[b]			
White (1988–1992)	46.9	38	15.1
Black (1983–1992)	29.4	20.8	10.6
England and Wales (1981–1990)	40.8	32.8	11.2
Cali Colombia (1982–1992)	42.8	31.5	23.3
Japan (1980–1992)	38.5	22.6	10.6
Estonia (1980–1989)	37	19.9	14.8
Israel Jews (1980–1989)	25.7	18.6	20.9
Non Jews (1980–1989)	27.8	16.2	28.7
Bulgaria (1980–1989)	33.2	18.5	18.4
India Bombay (1980–1992)	25.4	16.0	11
Ibadan Nigeria (1985–1992)	8.3	2.6	27.1

[a] Modified from Parkin DH, Kramarova GJ, Draper G, et al., editors. International incidence of childhood cancer, vol. II. Lyon: IARC Scientific Publications No. 144; 1998.
[b] SEER – North American 'Surveillance Epidemiology and End Results' Program.

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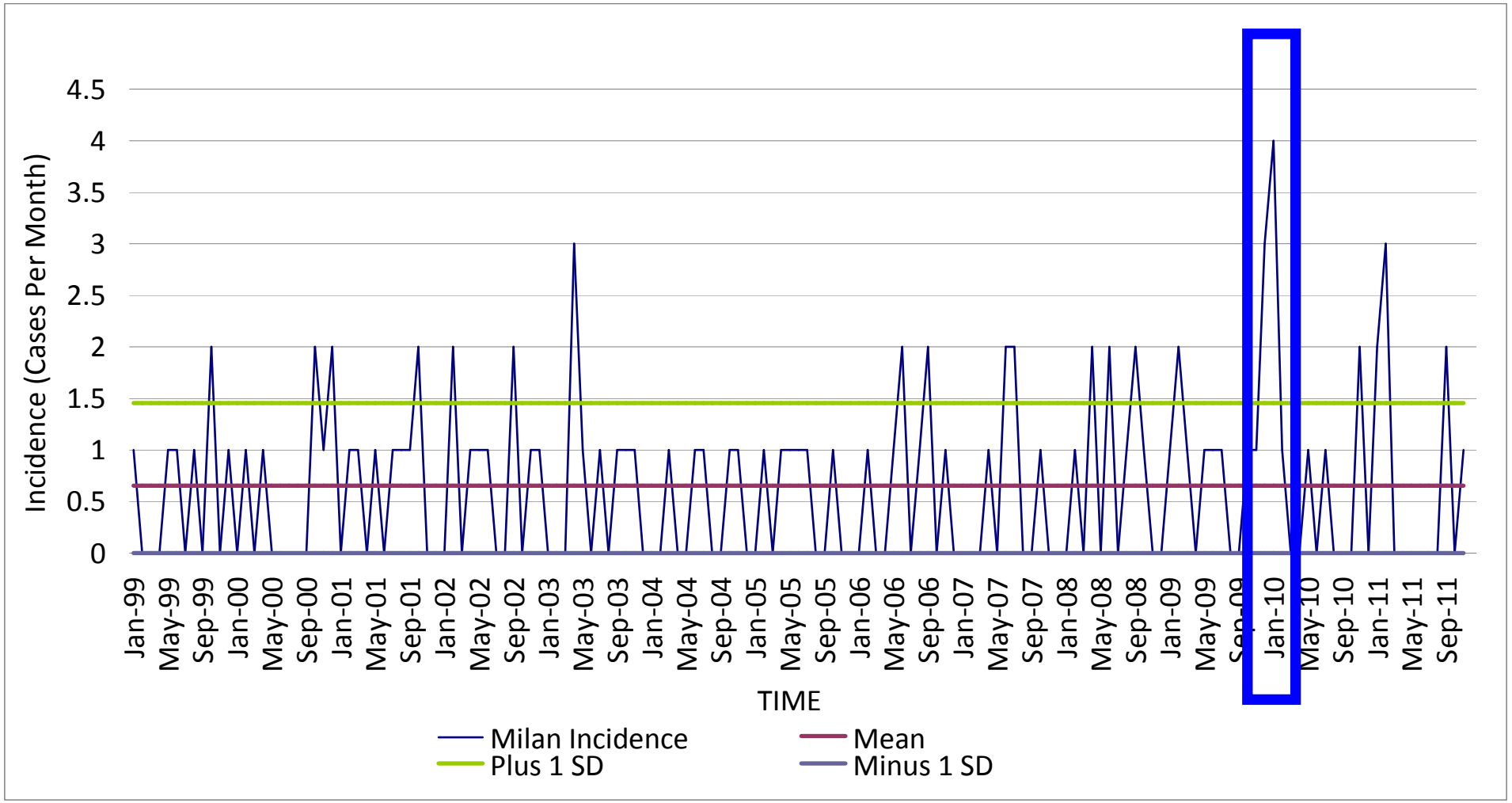
Deprivation increases the chance of greater infection exposure early in life and affluence reduces such exposure.

Major putative factors for causation of childhood leukaemia

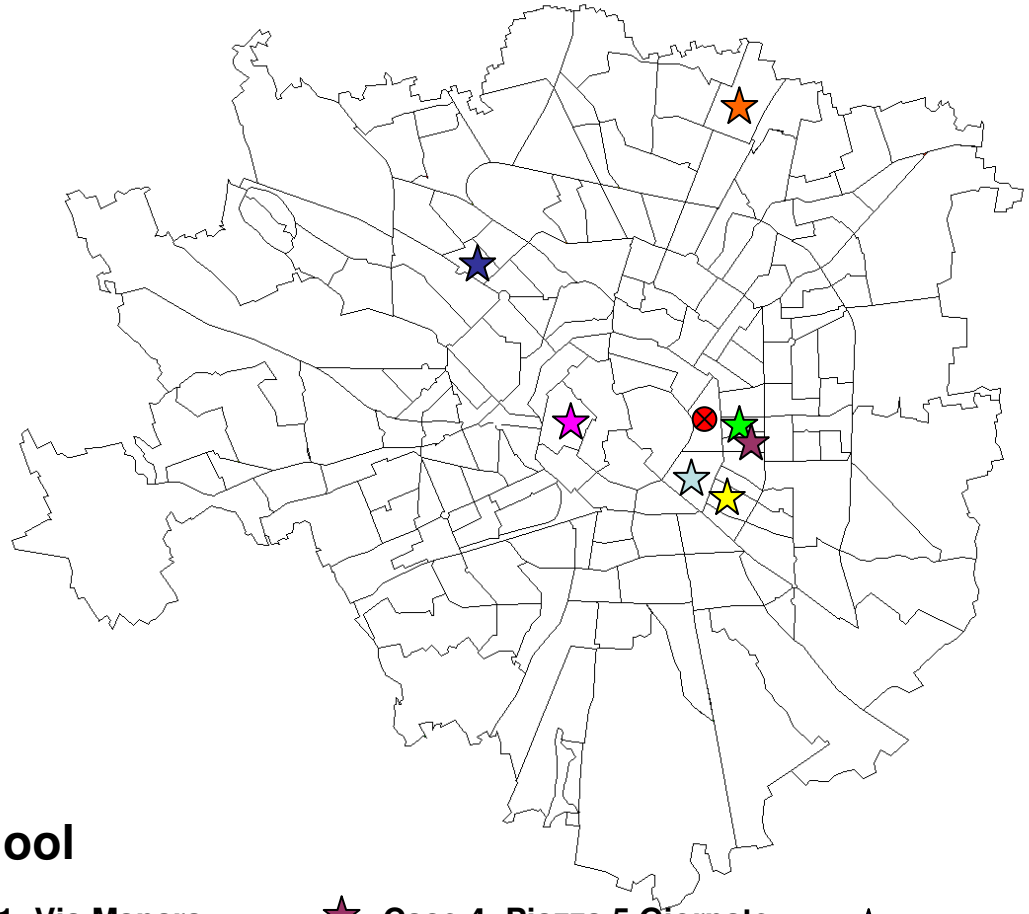
- Genetic predisposition
- Genetic susceptibility
- Environmental factors
  - Ionizing radiation
  - Non-ionizing electromagnetic fields
  - Chemicals/cytotoxics
  - Parental smoking/alcohol consumption
  - Perinatal and reproductive factors
  - Infections/response to infections

Childhood infections
Infections during pregnancy
Vaccinations
Day care attendance
High birth order
Breast feeding

Time series of ALL cases in Milan 1999-2011



Space distribution of ALL cases in Milan
December 2009 – January 2010



School

Case 1: Via Manara
Case 2: Via Properzio
Case 3: Via Poma
Case 4: Piazza 5 Giornate
Case 5: Viale Certosa
Case 6: Via Bignami
Case 7: Via Tamburini

December 2009-January 2010: a cluster of ALL in Milan?

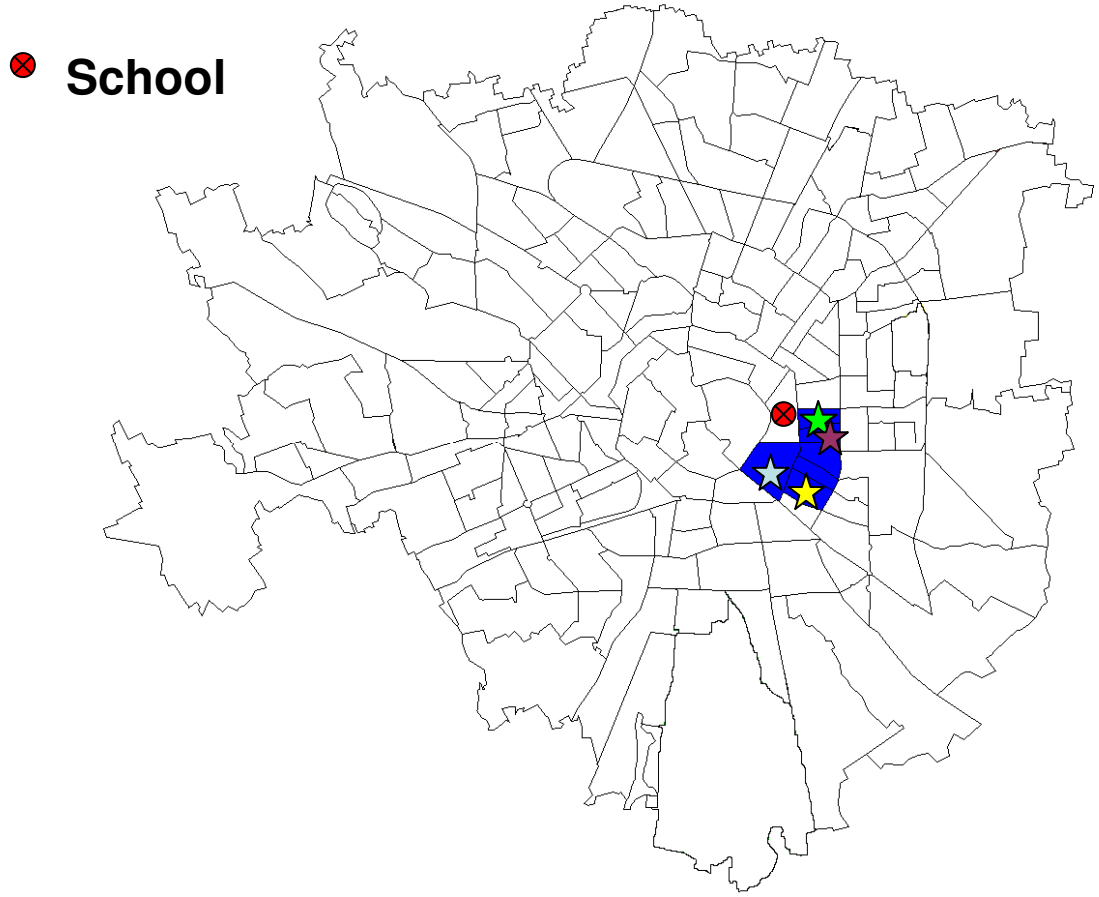
	SEX	Date of Diagnosis	Age at Diagnosis	Immuno-phenotype	t (9;22)	t(4;11)	t(12;21)	t(1;19)	Hyperdiploidy
1	F	14/12/2009	8	cALL	+	-	-	-	-
2	F	04/01/2010	6	cALL	-	-	-	-	-
3	M	14/01/2010	10	cALL	-	-	-	-	-
4	F	13/01/2010	2	cALL	-	-	-	-	+
5	M	15/12/2009	11	cALL	-	-	-	-	-
6	F	18/12/2009	5	cALL	-	-	-	-	+
7	F	12/01/2010	5	cALL	-	-	+	-	-

Cases n. 1, 2, 3, 4, 5, 6, 7: same town.
Cases n. 1, 2, 3, 4: same town and area
Cases n. 1, 2, 3; same town, area, and school

- Varying ages at diagnosis (2-11 years)
- All were B precursor ALL in immunophenotype.

- Analysis of chromosomal abnormalities did not reveal common features
- Inherited leukaemia associated alleles did not show an augmented risk

Space-time cluster identified by Scan Statistic



Time period:
Dec 2009 – Jan 2010

Observed cases = 4

Expected cases = 0.04

P-value=0.026

Diagnoses of cases focussed in a 4 week-period in children of different ages (2-11yrs):

→ **A common , but transient , promotional exposure very proximal (or close) in time (weeks/months) to the diagnoses?**

Investigation plan: looking for risk factors

- Field measurements for ionizing and non-ionizing radiations, and chemical risk factors:
  - Schools (both the renovated and the temporal)
  - Prevalent house of residence
- Other investigations:
  - School refurbishment: classification of materials used to renovate with attention to adhesives and paints
  - School canteen: chemical and microbiological analysis of foods and water
- Anamnestic questionnaire on personal and family history:
  - Past exposure to chemical & physical agents
  - Lifestyle habits (pregnancy and early life)
  - Hygiene hypothesis variables
  - Cancer family history

SETIL study: Italian epidemiological study on the aetiology of childhood leukaemia, lymphoma and neuroblastoma

Investigation plan: main results

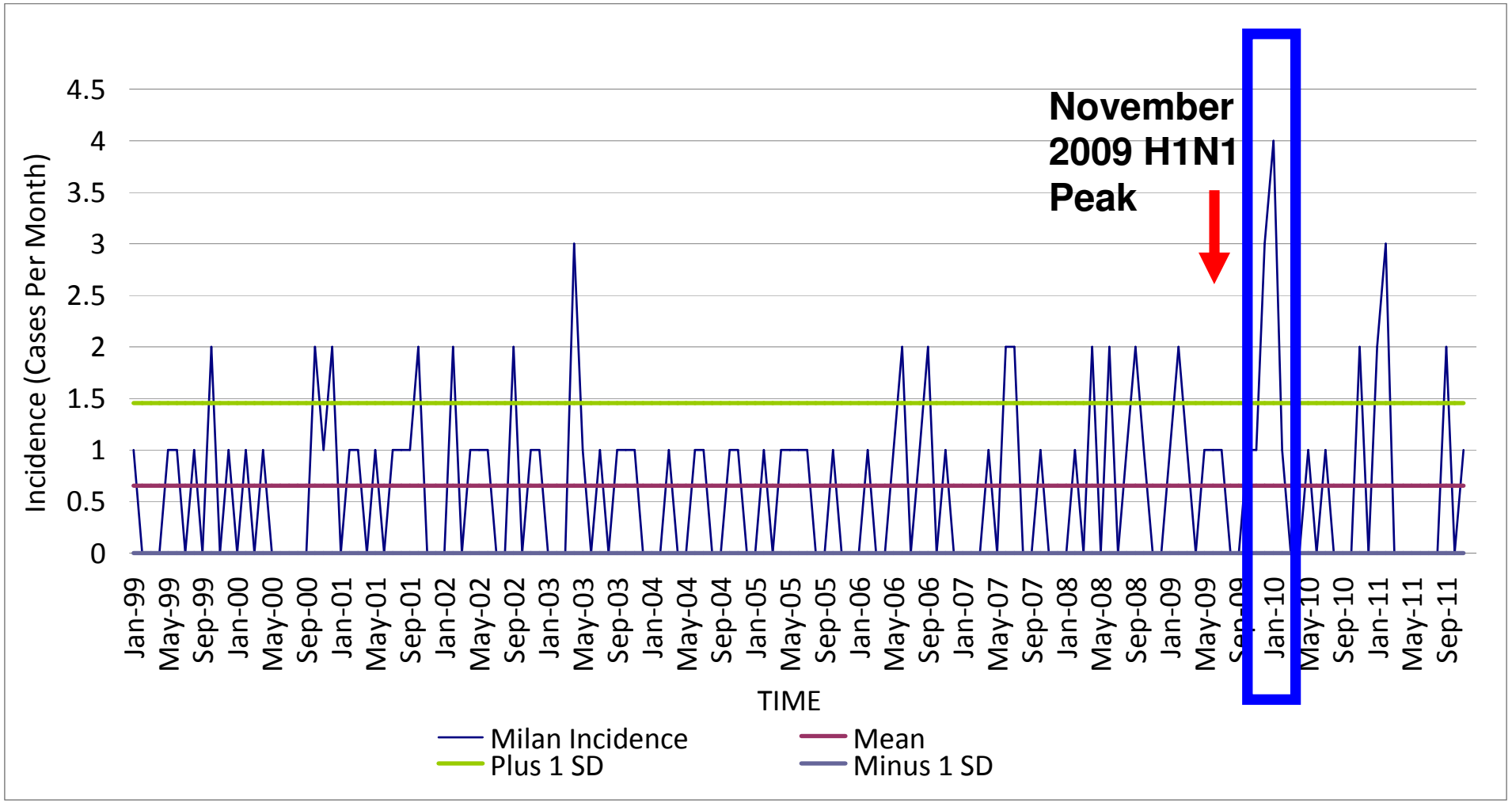
In the 2 schools and in the houses of children we measured

- radio frequencies (RF)
- extremely low frequency magnetic fields (ELF)
- indoor gamma radiations
- indoor benzene and formaldehyde concentrations
- ……

All the values measured were comparable among them and were in the range of values normally present in environments for similar use.

Also the results from SETIL questionnaire did not report any situation different from expected values. ?

ALL cases in Milan: H1N1 pandemia



H1N1 hypothesis: a trigger to overt leukaemia

-"New" virus

- Synchronization of ALL diagnoses following flu peak

-100% of ALL cases affected by flu
(vs. 32 % in general pop. same age)

- Harvesting effect

Why this school?

→ High socio-economic status of families

→ High birth order of ALL cases

→ Paucity of infectious exposures in the first year of life

Conclusions

- A statistically significant space-time cluster of childhood ALL cases in Milan
- All postulated etiological factors were investigated
- The exposure to a new infectious agent (A-H1N1 virus) seems to be the most likely trigger for the cluster cases
- Results are compatible with the ‘delayed infection’ hypothesis for which an abnormal immune or inflammatory response to a common infection promotes ALL in susceptible individuals.

Thanks!

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