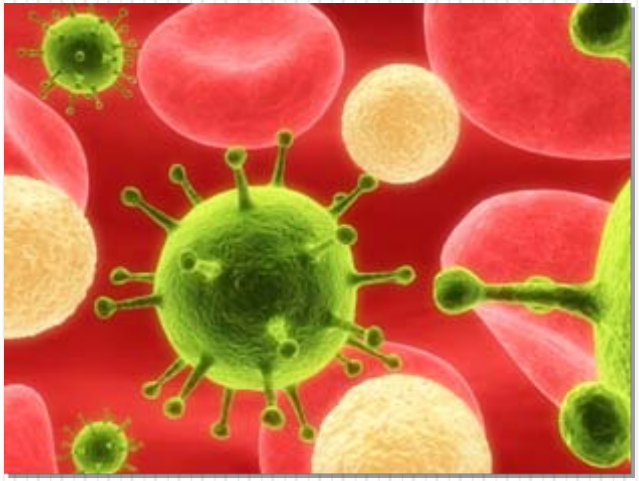
Epidemiological Evidence Supporting a Role for Infections in Childhood Cancer Risk



Childhood Cancer 2012
London, UK
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Outline

- History and burden of infections on human cancers
- Agents identified in childhood cancers
- Childhood leukemia and exposure to infections
  - ✓Delayed infection hypothesis (Greaves, 1988)
  - ✓Population mixing hypothesis (Kinlen, 1988)
  - ✓Challenges to establishing an infective basis
- Childhood brain and other tumors and infections
- Concluding remarks

Identification of Infectious Agents in Cancer

- In 1911, 1st tumor virus discovered by Peyton Rous
  - ✓ Rous sarcoma virus (RSV) = RNA tumor virus

- In 1965, 1st human tumor virus by Epstein and Barr
  - ✓ EBV = Burkitt lymphoma

- In 1968, hepatitis B virus (HBV) discovered = serum hepatitis
  - ✓ HBV infection and hepatocellular carcinoma (HCC), 1975

- In 1974, HPV and cervical cancer substantiated by Harald zur Hausen

1910

1920

1940

1960

1980

2000

- Non-viral agents: *H. pylori*, blood and liver flukes

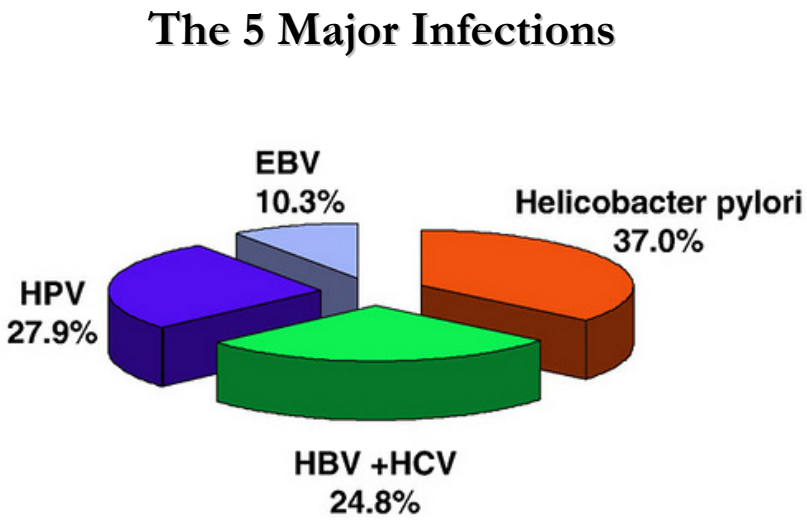
- In 1980, 1st human retrovirus -- HTLV-1; In 1981, linked to adult T-cell leukemia

- In 1989, hepatitis C virus (HCV) linked to HCC
- In 1994, Kaposi's sarcoma herpesvirus (KSHV) linked to Kaposi's sarcoma

Source: Javier and Butel, Cancer Research, 2008

Global Burden of Infection Agents on Cancer

Agent	Cancer
H. pylori	Stomach, lymphoma
HPV	Cervix, ano-genital, mouth, pharynx
HBV and HCV	Liver
EBV	Nasopharynx, Hodgkin, Burkitt
HIV/KSHV	Kaposi
Schistosomes	Bladder
HTLV-1	Adult T-cell leukemia
Liver flukes	Liver



Source: zur Hausen, Virology, 2009

- Infection attributable cancer in 2002: 17.8%
- If infectious diseases prevented:
  - 26.3% fewer cases in developing countries
  - 7.7% fewer cases in developed countries

Source: Parkin, Int J Cancer, 2006

Mechanisms

Direct Carcinogen

Mechanism	Example
Introduction of viral oncogenes into host cell	HPV, EBV, KSHV, HTLV-1
Modified viral oncogenes after integration into host cell	Merkel cell polyomavirus

Indirect Carcinogen

Mechanism	Example
Virus-induced immunosuppression activates other tumor viruses	HIV
Chronic inflammation, induction of oxygen radicals	HBV, HCV, H. pylori, parasites
Induction of mutations, chromosomal instability and translocations	Adenoviruses, herpesviruses, TT virus, etc.

Reference: zur Hausen, Virology, 2009

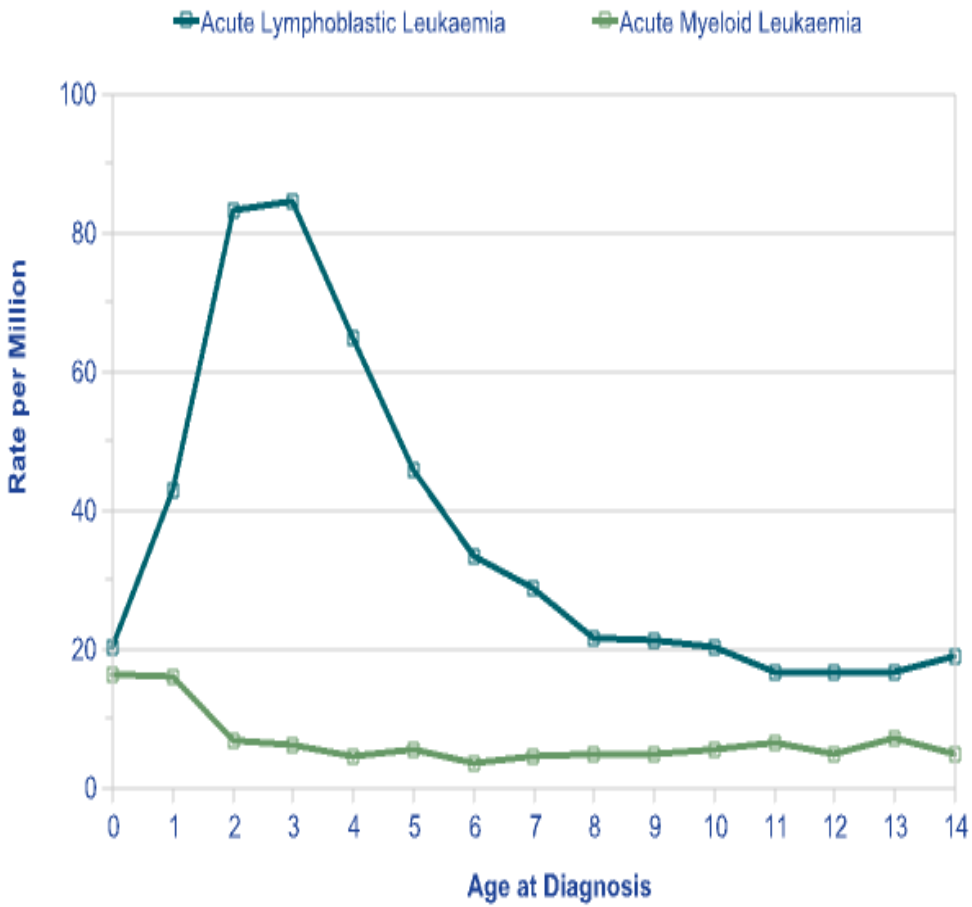
Childhood Leukemia

Delayed Infection (Greaves)

Population Mixing (Kinlen)

Suggestions from Descriptive Evidence *(Delayed Infection Hypothesis)*

Average Annual Age-Specific Incidence Rates, Great Britain, 1996-2005



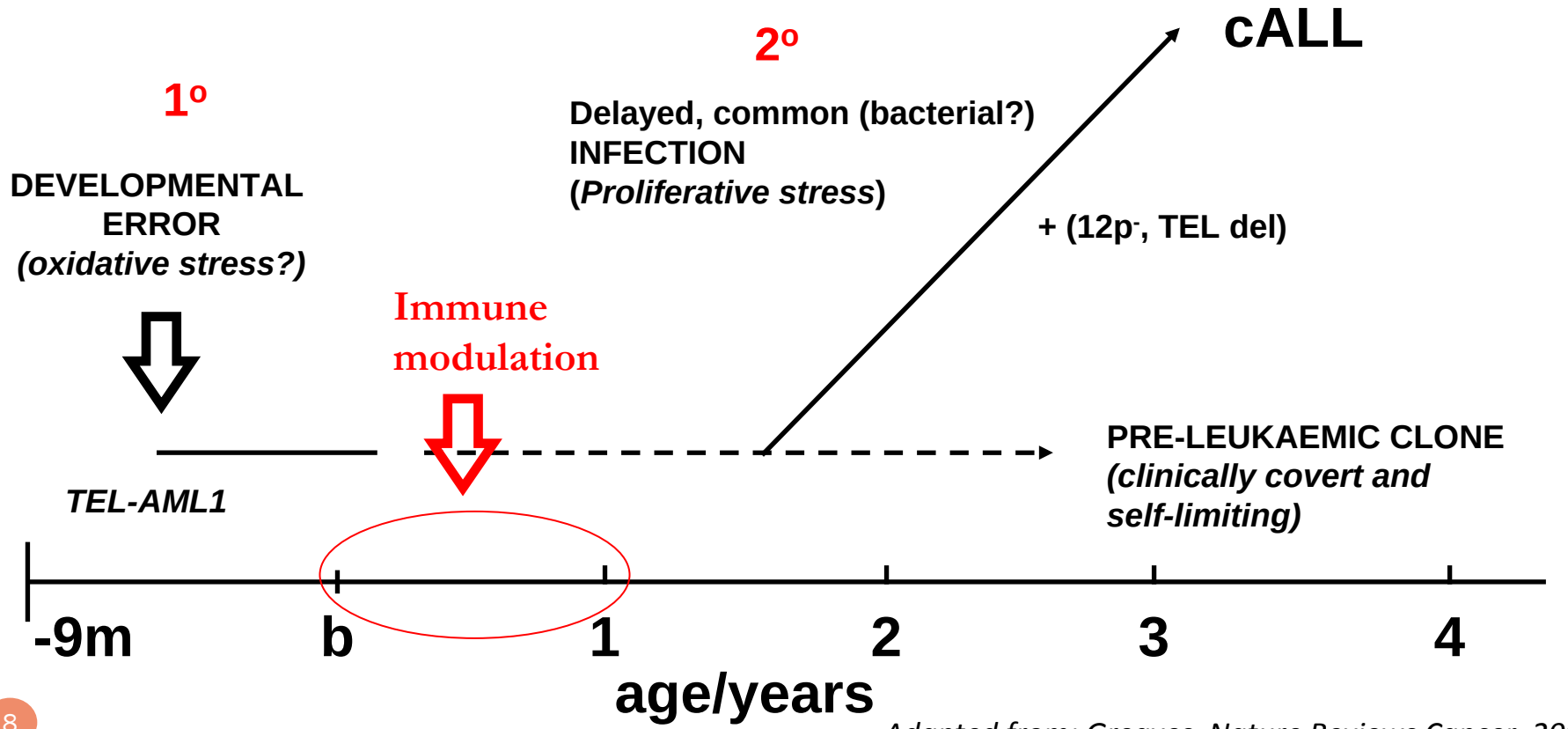
Source: Cancer Research UK

- Similar to childhood infections
- Marked peak only in the more developed regions
- Rising incidence mostly in developed regions of world
- Peak mostly pre-B ALL (cALL)

Refs: Greaves et al., Leukemia Research, 1985
Parkin et al., IARC , 1998

Delayed Infection Hypothesis (*Greaves hypothesis, 1988*)

- Childhood ALL is the result of an adverse immune response to common infections resulting from insufficient priming of the immune network early in life.



Adapted from: Greaves, Nature Reviews Cancer, 2006

Proxy Measures (indirect)

- Contact with other children is the main source of exposure to common infections
  - ✓Daycare attendance
  - ✓Birth order
  - ✓Reported infections in infancy

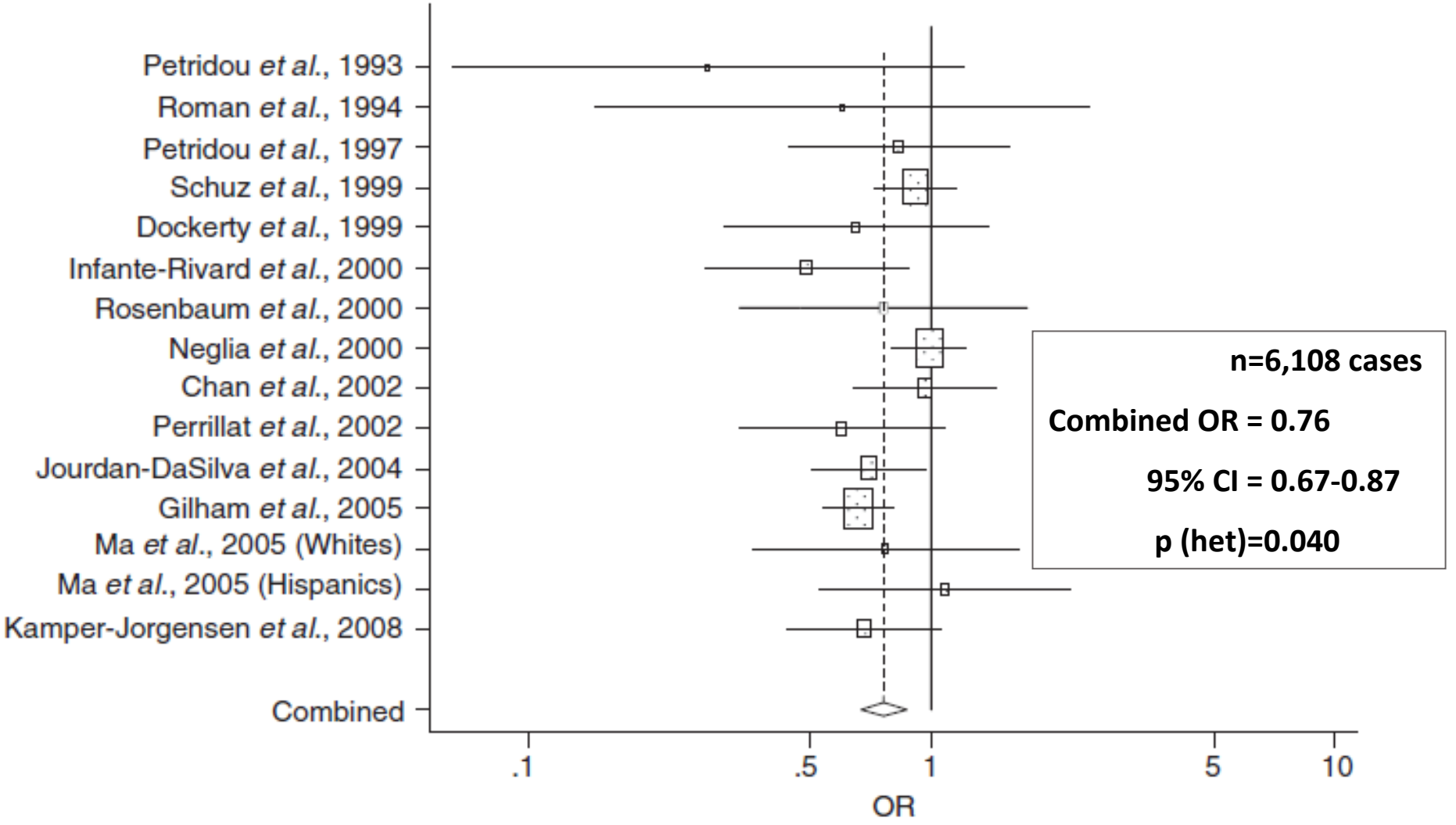
- A reduced risk of childhood ALL associated with:
  - ✓Daycare attendance in infancy
  - ✓Higher birth order
  - ✓More reported common infections in infancy

14 Daycare Attendance Studies

Study, Year	Exposure Type	Time of Exposure
Petridou et al., 1993	Attendance at creche (No/Yes)	< 2 yrs of age
Roman et al., 1994	Preschool playgroup (No/Yes)	Year before dx
Petridou et al., 1997	Day care (No/Yes)	Birth to dx
Schuz et al., 1999	Deficit in social contacts (No/Yes)	< 2 yrs of age
Dockerty et al., 1999	Reg. contact outside home (No/Yes)	< 1 yr of age
Infante-Rivard et al., 2000	Entry ≤2 yrs old vs. no day care	< 2 yrs of age
Rosenbaum et al., 2000	>36 mo. of care vs. stayed home	Birth to dx
Neglia et al., 2000	Day care before age 2 (No/Yes)	< 2 yrs of age
Chan et al., 2002	Index & family day care measure	< 1 yr of age
Perrillat et al., 2002	Day care (No/Yes)	Birth to dx
Jourdan-Da Silva et al., 2004	Day care (No/Yes)	Birth to dx
Gilham et al., 2005	Social activity (No/Yes)	< 1 yr of age
Ma et al., 2005 (NH-Whites)	Day care (No/Yes)	< 1 yr of age
Ma et al., 2005 (Hispanics)	Day care (No/Yes)	< 1 yr of age
Kamper-Jorgensen et al., 2008	Child care (No/Yes)	< 2 yrs of age

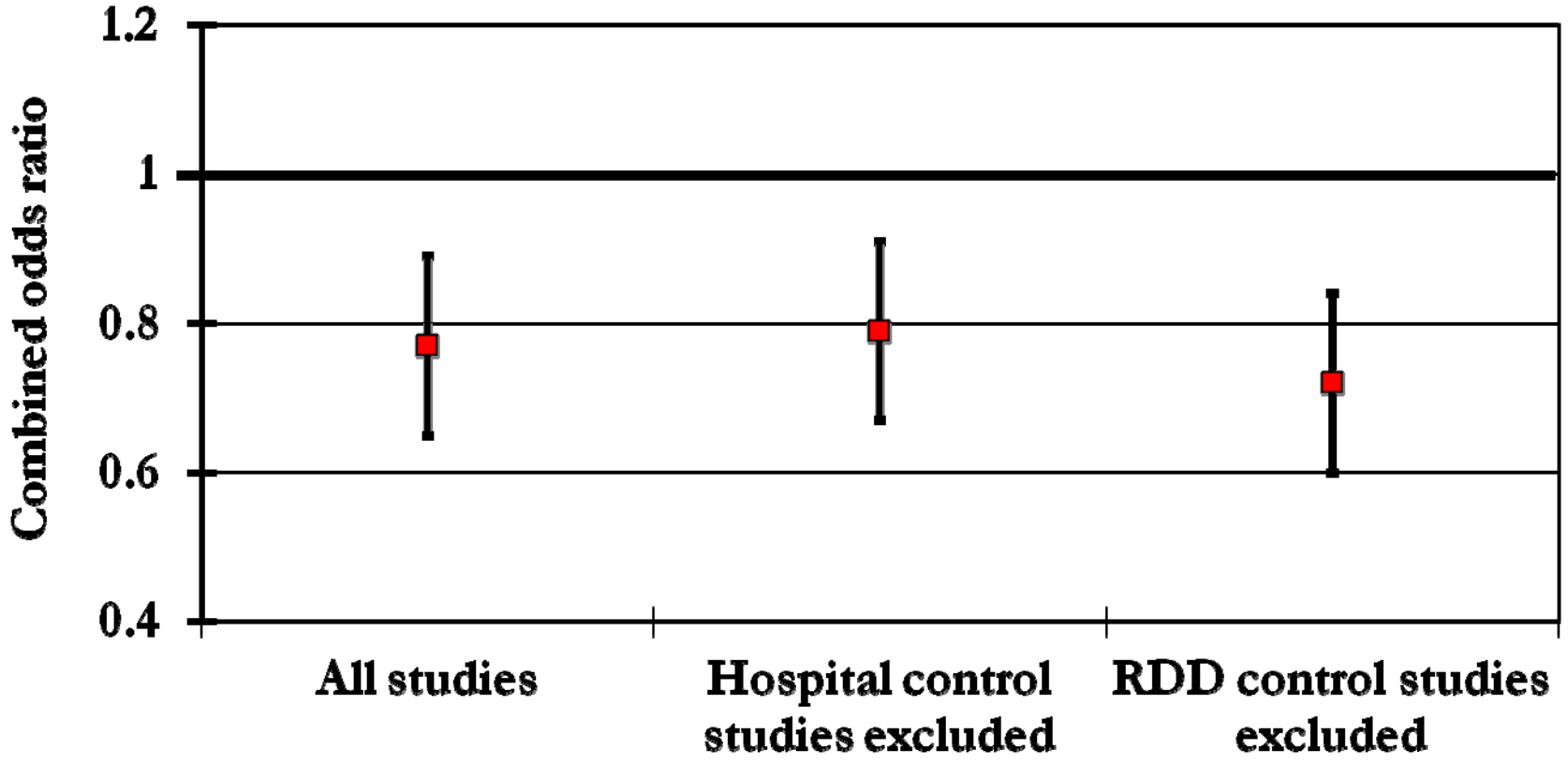
Daycare Attendance and Childhood ALL

(Meta-Analysis)

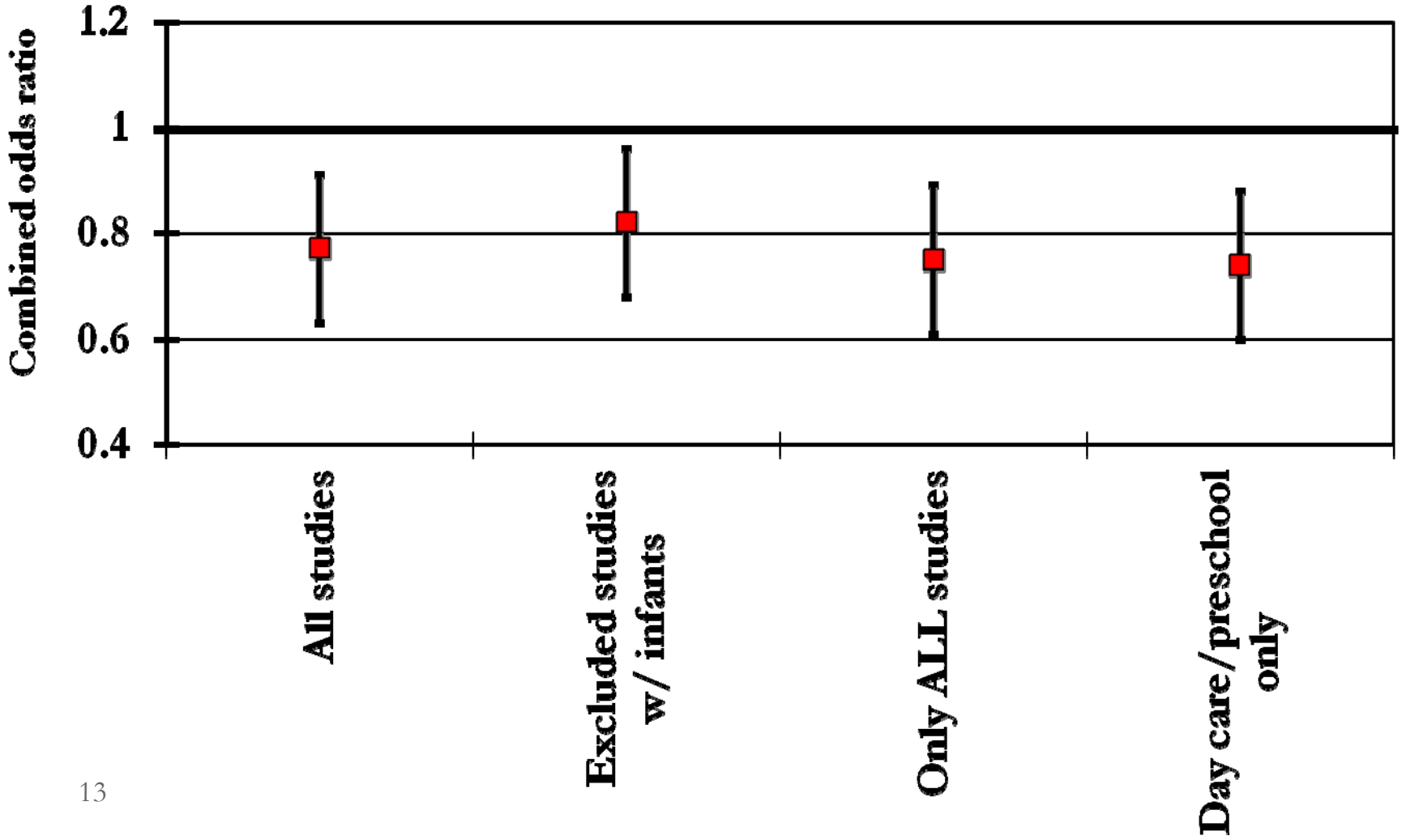


Ref: Urayama et al., Int J Epidemiology, 2010

Heterogeneity: *Selection Bias*



Heterogeneity: *Information Bias*



Self-reported Infectious Disease History

Author (year)	Country	N cases	Exposure	OR (95% CI)
Van Steensel-Moll (1986)	The Netherlands	492	Any infections 1st year	0.6 (0.4-1.0)
Perrillat (2002)	France	129	Repeated infections <age 2	0.6 (0.4-1.0)
Chan (2002)	Hong Kong	98	Any infection 1st year	0.7 (0.4-1.2)
Rudant (2010)	France	517	Repeated infection 1st year	0.7 (0.6-0.9)
Jourdan-Da Silva (2004)	France	334	Repeated infection 1st year	0.8 (0.6-1.0)
Neglia (2000)	USA	727	Ear infection <age 2	0.8 (0.6-1.1) Ptrend=0.03
Rosenbaum (2005)	USA	255	Ear infection <age2	1.2 (0.9-1.7)
Dockerty (1999)	New Zealand	116	Any infection 1st year	1.4 (0.8-2.4)

Delayed Infection Hypothesis and ALL in the CCLS

Social contacts and ear infection variables	Model 3[1] OR (95% CI)	*p*
Non-Hispanic White		
Daycare child-hours[2] by age 6 months	0.83 (0.73–0.94)	0.004
Older siblings (yes *vs.* no)	0.59 (0.43–0.83)	0.002
Daycare child-hours*older siblings interaction	–	–
Ear infections (*vs.* none during 1st year)		
Age <6 months only	0.44 (0.19–1.02)	0.056
Age 6–11 months only	0.71 (0.46–1.08)	0.110
Both time periods (<6 and 6–11 months)	1.32 (0.83–2.11)	0.247
Hispanic		
Daycare child-hours[2] by age 6 months	1.06 (0.91–1.23)	0.443
Older siblings (yes *vs.* no)	0.84 (0.62–1.13)	0.250
Daycare child-hours*older siblings interaction	–	–
Ear infections (*vs.* none during 1st year)		
Age <6 months only	0.45 (0.25–0.79)	0.006
Age 6–11 months only	0.82 (0.56–1.20)	0.304
Both time periods (<6 and 6–11 months)	1.05 (0.67–1.64)	0.839

- Reduced risk associated with all three measures
- No interaction between social contact measures
- No association for social contact measures
- Reduced risk associated with ear infections
- Assumptions for social contact measure not met in Hispanics?

Ref: Urayama et al., Int J Cancer, 2010; Ma et al., CEBP, 2005

Population Mixing (*Kinlen Hypothesis*, 1988)

Sellafield (Seascale, W. Cumbria)

Dourneay (Thurso, Scotland)

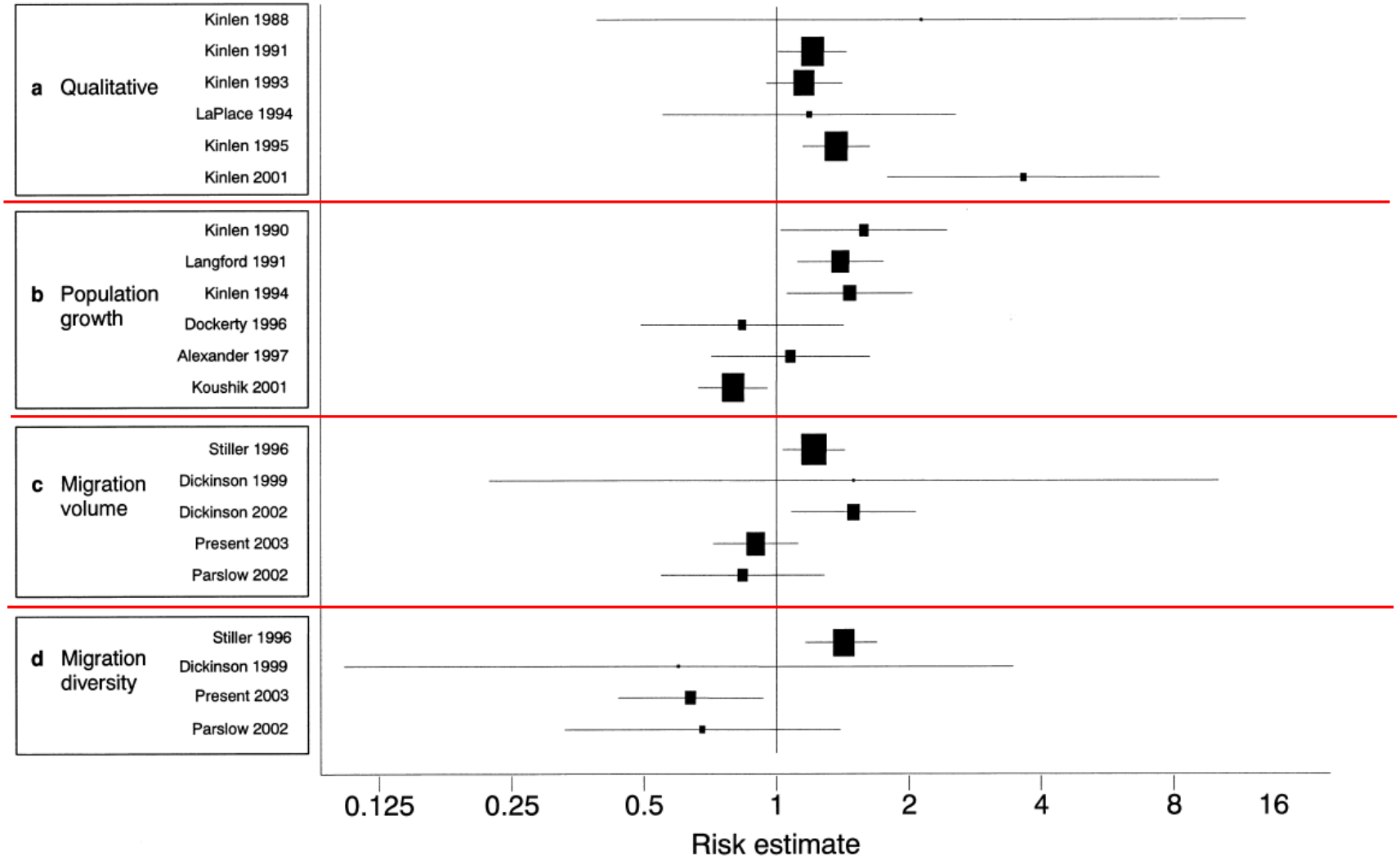
- The excess of childhood leukemia was observed as a rare outcome under conditions of population mixing where relatively isolated communities were exposed to new infections to which they were non-immune.
  - ✓ Likely a specific (viral) agent
  - ✓ Focuses on rural population mixing– *A testable situation*
  - ✓ 'Population mixing' is a crude risk factor and may not produce the critical level of relevant contacts necessary for an epidemic in all situations.

Rural Population Mixing Tested

- Rural new towns (*Kinlen et al., 1990*)
- Wartime evacuation of children to rural areas (*Kinlen and John, 1994*)
- Post-war increases of national servicemen to rural areas (*Kinlen and Hudson, 1991*)
- Rural Scottish communities from which many men worked away from home in the North Sea oil industry (*Kinlen et al., 1993*)
- Commuting increases (*Kinlen et al., 1991*)

- Studies of rural population mixing outside the UK have also shown excess of childhood leukemia.
  - ✓Canada (*Koushik et al., 2001*); Hong Kong (*Alexander et al., 1997*); France (*Boutou et al., 2002*); Greece (*Kinlen and Petridou, 1995*); United States (*Wartenberg et al., 2004*)

Studies of Residential Population Mixing



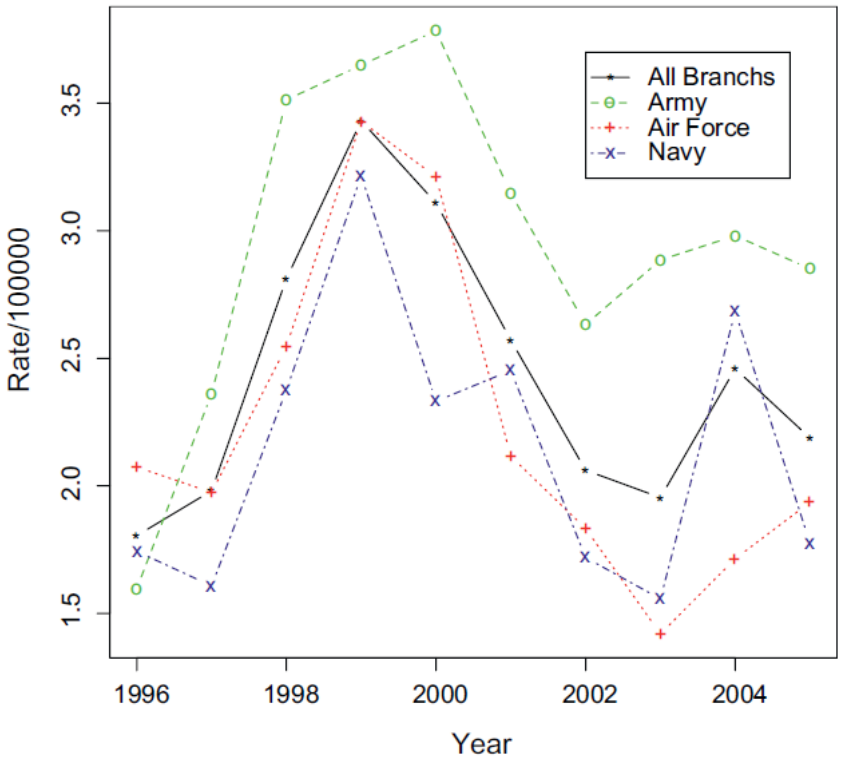
Ref: Law et al., Am J Epidemiology, 2003

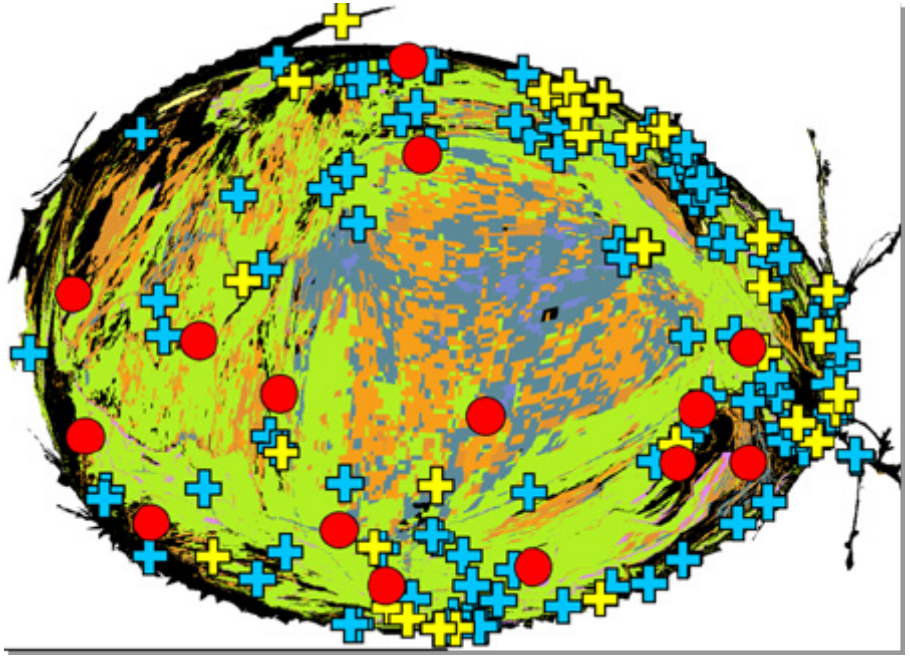
Population Mixing and Fallon, Nevada

- 14 children were diagnosed with ALL during 1997-2003
  - ✓ Based on population at risk, 1 case expected every 2 years
  - ✓ RR=12 if child resided in Churchill county during this period *(Steinmaus et al., EHP, 2004)*
- Unique characteristics of Fallon
  - ✓ Wetlands and land suitable for agriculture
  - ✓ Nature arsenic, tungsten, and radioactive minerals
  - ✓ Navy training facility and hard metal refining factory
- Population mixing *(Kinlen and Doll, BJC, 2004)*
  - ✓ US 2000 census: population of 7,536
  - ✓ Military personnel temporarily assigned
    - 20,000/year in early 1990s; 55,000 in year 2000
  - ✓ Indirect exposures through schools and civilian workers at base, etc.
  - ✓ Predict that any epidemic would initially be among trainees then secondarily to local residents

Fallon Study *(S. Francis et al., 2012)*

Age-adjusted childhood ALL rates among military





- Unusual space-time patterning is consistent with an involvement of an infectious disease.
- Concordant temporal pattern of childhood leukemia rates among military may suggest it as the source of infection
- Mosquitoes may be one route of transmission of infection
- Transmission of this “new” infection to “susceptibles” led to excesses in leukemia

Lack of direct evidence and limitations

- A specific transforming agent has NOT been identified despite intensive efforts *(MacKenzie et al., 2006)*
- 'Childhood leukemia as a rare response to one or more common infections acquired by personal contact under modern socio-demographic circumstance' *(Greaves, 2006)*
- Consensus on the infective basis of childhood leukemia has been affected by limitations in exposure assessment
- Disparity between self-report versus records-based studies

Clinically Diagnosed Infections and ALL

- Clinically diagnosed infections in infancy is associated with an increased risk of childhood ALL age 2-5 years *(Roman et al., AJE, 2007)*
- More than 25% of mothers who took child to GP with an infection did not report doing so at interview *(Simpson et al., EJC, 2007)*

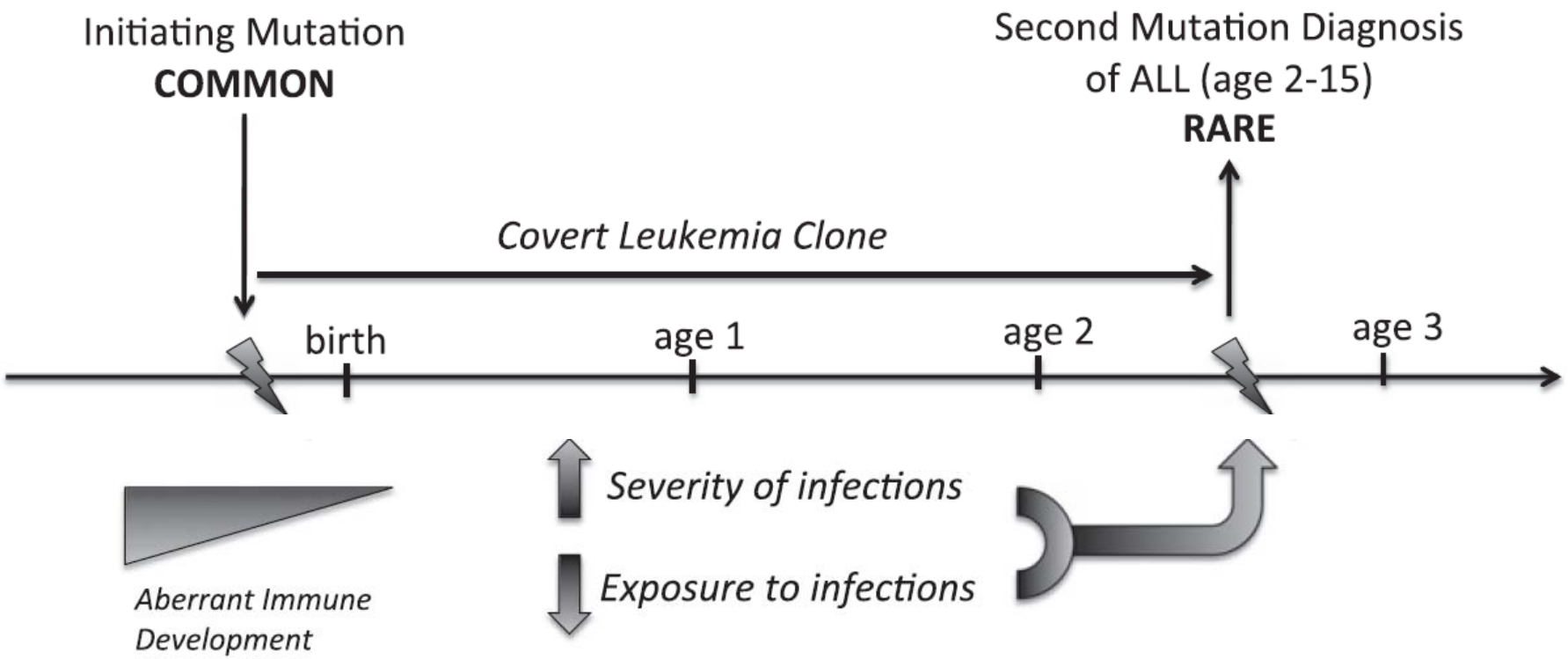
Maternal report of illness with confirmatory GP visit		GP Infection Record			GP infe
		Controls			
Maternal Report		Yes	No	Sensitivity (%)	PPV[a] (%)
Any infection					
Yes	1,055	758	118	71.9	86.5
No		297	115		
Eye infection					
Yes		149	122	39.3	55.0
No		230	787		
Ear infection					
Yes		84	146	35.3	36.5
No		154	904		

a PPV, positive predictive value.

Dysregulated Immune Response and IL10

- A dysregulated immune response to infection during 1st few months of life promote subsequent genetic events leading to childhood ALL.
- An altered "congenital responder status" to infections? *(Wiemels, 2012; Dorak et al., 2007)*
- IL-10: a key regulator in modulating the intensity and duration of immune response to infections
- Children with ALL had lower neonatal levels of IL10; suggests that the dysregulated immune function of children with ALL is present at birth *(Chang et al., CEBP, 2011)*
- This has been replicated in an independent series of cases and controls in the *CCLS (de Smith et al., CwC poster)*

2 Mechanisms Explaining ↑ and ↓ Risk of ALL



Source: Fig.3- Wiemels, Chem Biol Interact, 2012
Greaves, Nature Reviews Cancer, 2006

Childhood CNS Tumors and Infection

- Infectious exposures occurring during pregnancy and perinatal period (e.g. viral infections)

  (Linet et al., 1996, Linos et al., 1998; Fear et al., 2001; Dickinson et al., 2002)

- Viral genomic sequences detected in certain CNS tumor subtypes (polyomaviruses)

  (Krynska et al., 1999; Kim et al., 2002)

- Studies using proxy measures are inconsistent

  (Shaw et al., 2006; Schmidt et al., 2010)

  - Evidence from space-time clustering and seasonality

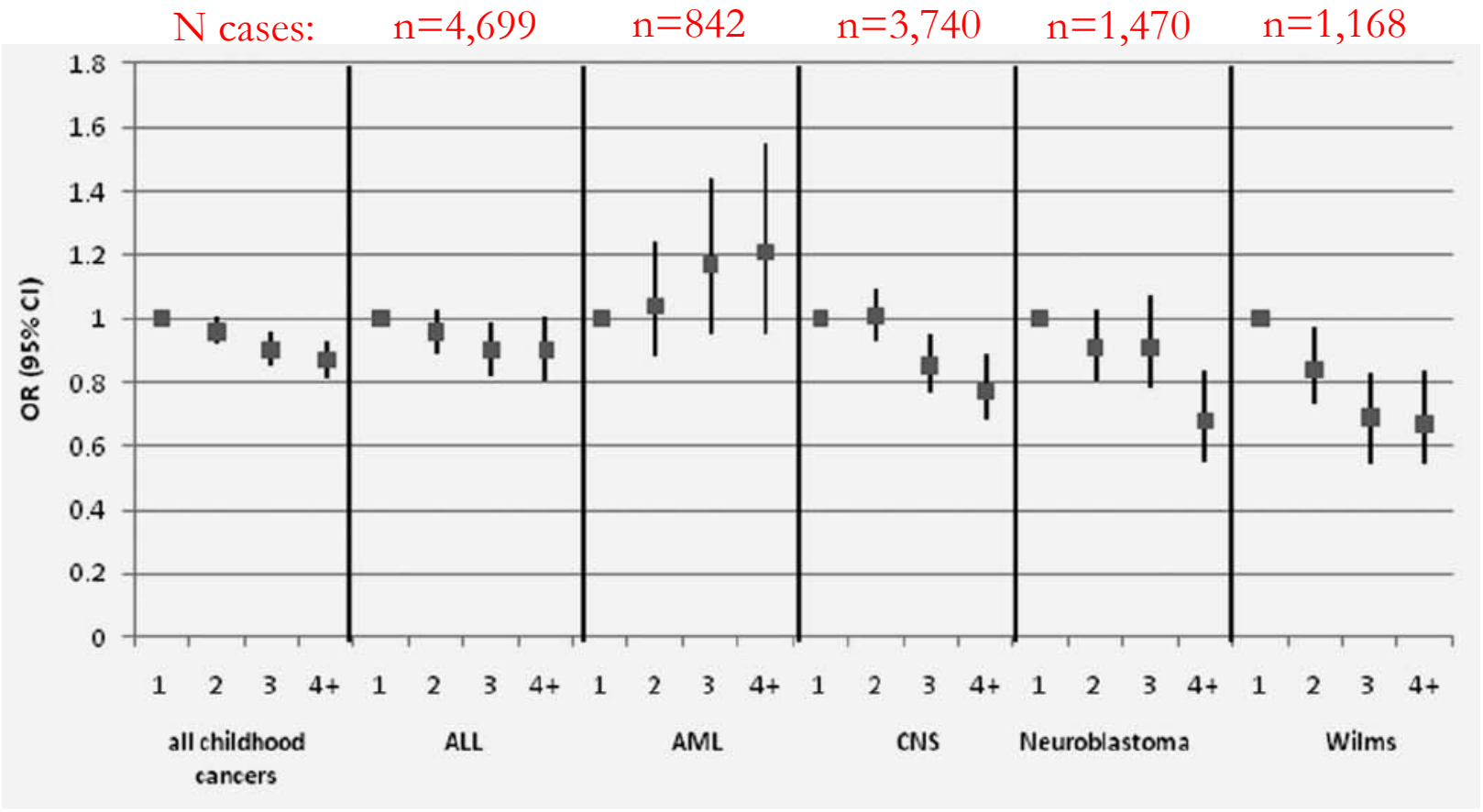
  (McNally et al., 2002, 2008)

- Cross-space-time clustering of childhood ALL and astrocytoma

  (McNally et al., EJC, 2005)

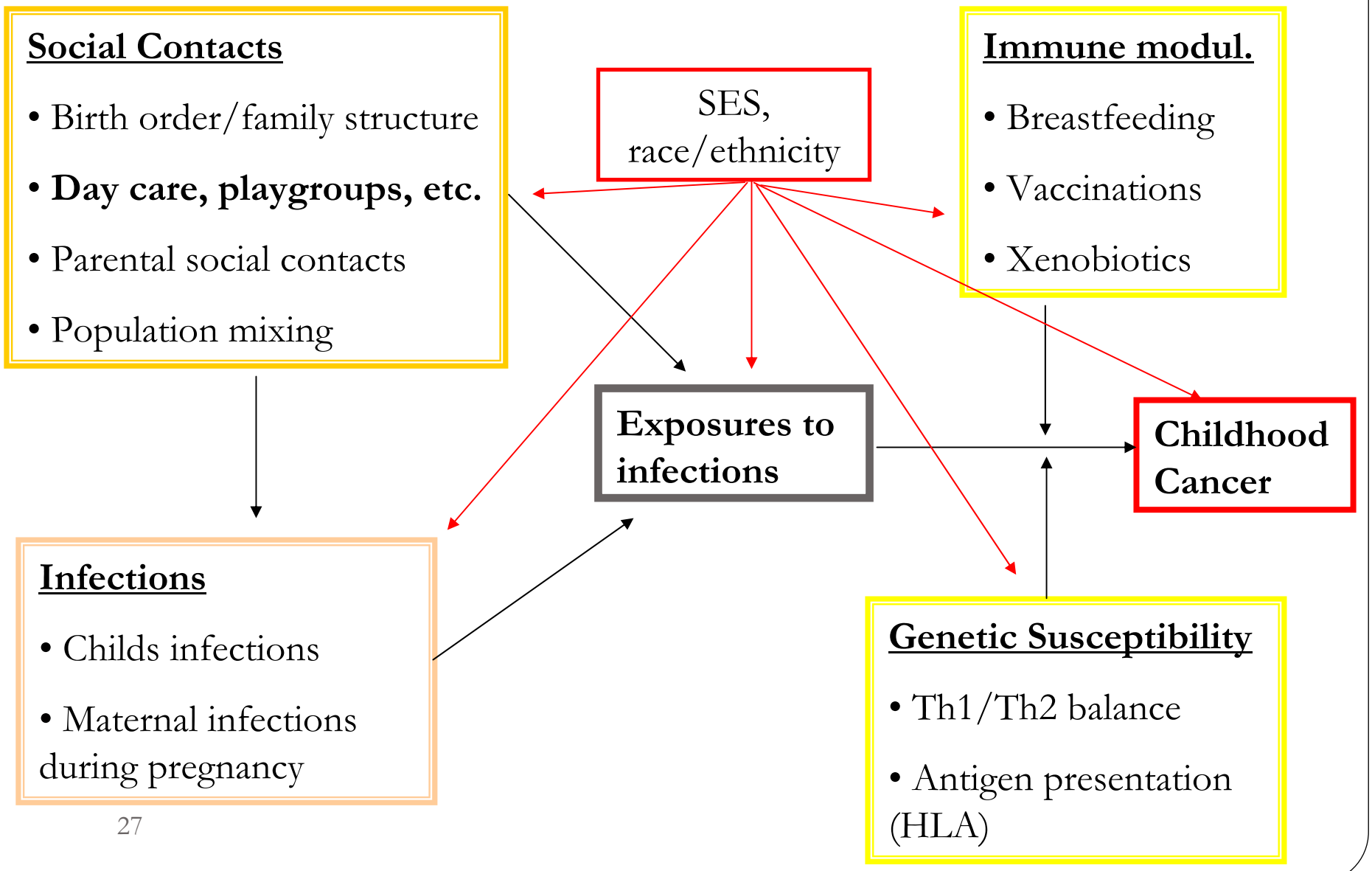
Birth Order Associations across Childhood Cancer Types

- Pooled case-control study (5 studies); 17,672 cases: 57,966 controls
- Overall inverse association between childhood cancer and ↑ birth order



Ref: Von Behren et al., Int J Cancer, 2011

Complexity of Relationships



Concluding Remarks

- Evidence of a role for infections and immune response in lymphomas and neuroblastoma, as well.

- *Childhood Leukemia and immune-related evidence is abundant (McNally and Eden, BJH, 2004)*
- Other hypotheses in childhood leukemia
  - ✓ *Smith hypothesis- in utero* exposures *(Smith, J Immunotherapy, 1997)*
  - ✓ *Adrenal hypothesis-* ↑ cortisol levels *(Schmiegelow et al., Leukemia, 2008)*
  - ✓ *Infective lymphoid recovery hypothesis- (Richardson, Leuk Research, 2011)*

- Genetic variation and risk, together with exposure data
- Maximize opportunities for consistency across studies
  - ✓ Coordinated studies and consortia

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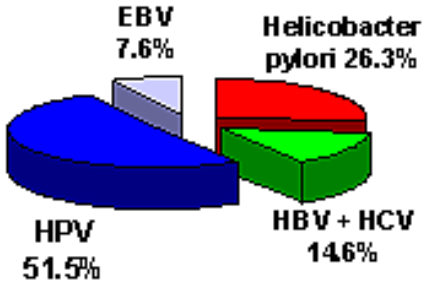
Thank you for your attention!

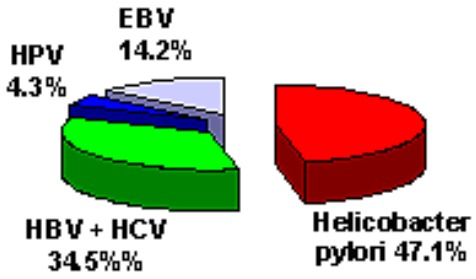
Females: Annual Global Cancer Incidence due to Infections

1 006 544 = 19.9% of total cancer incidence in females



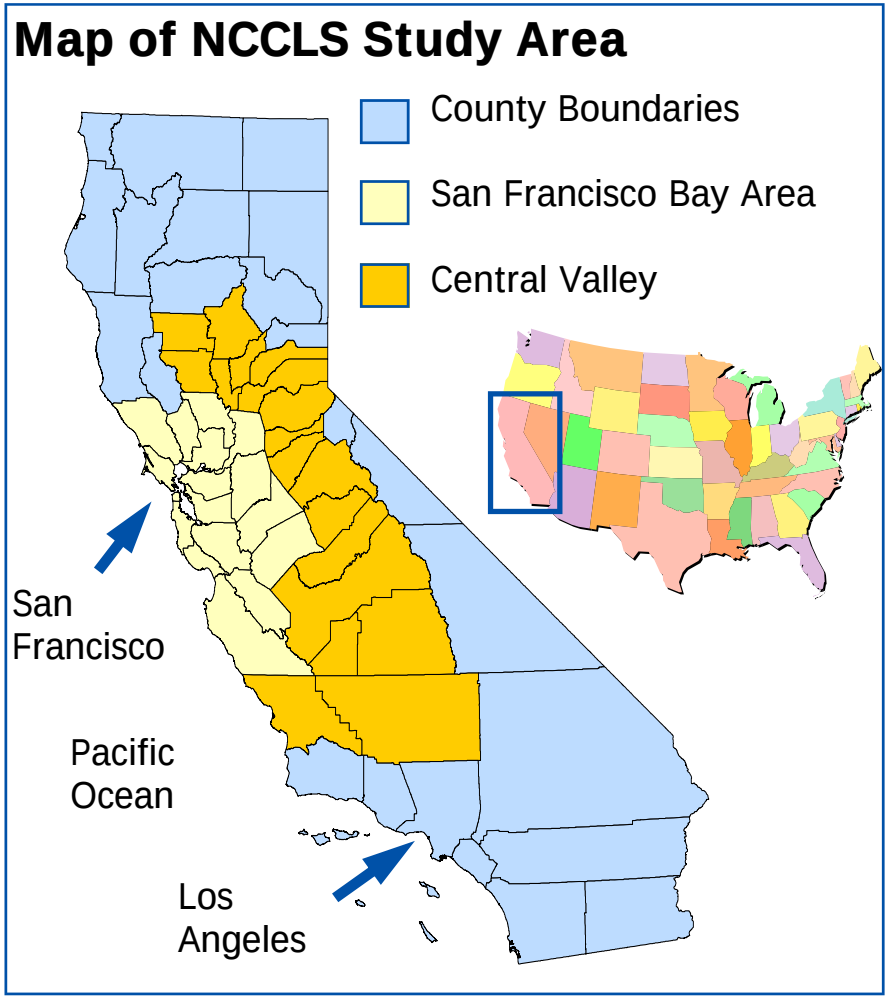
Males: Annual Global Cancer Incidence due to Infections

1 025 524 = 17.7% of total cancer incidence in males



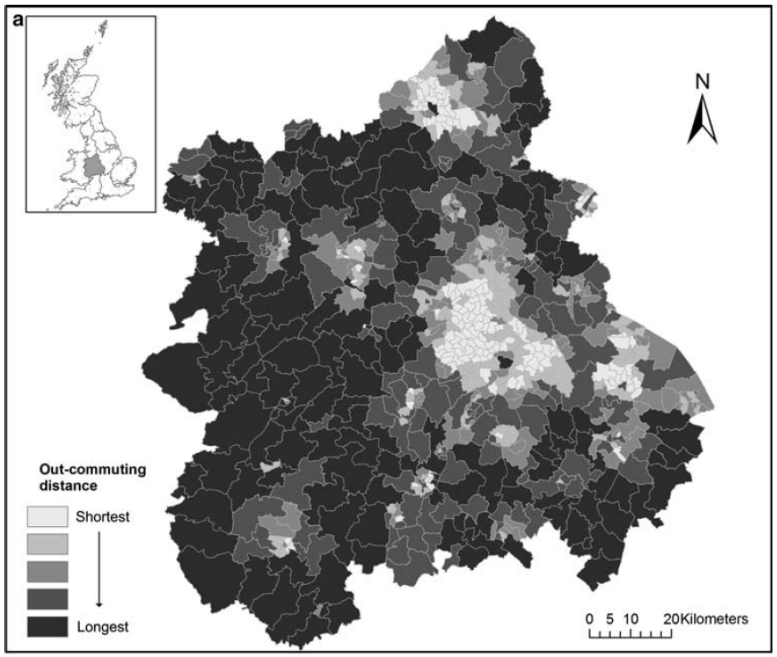
California Childhood Leukemia Study

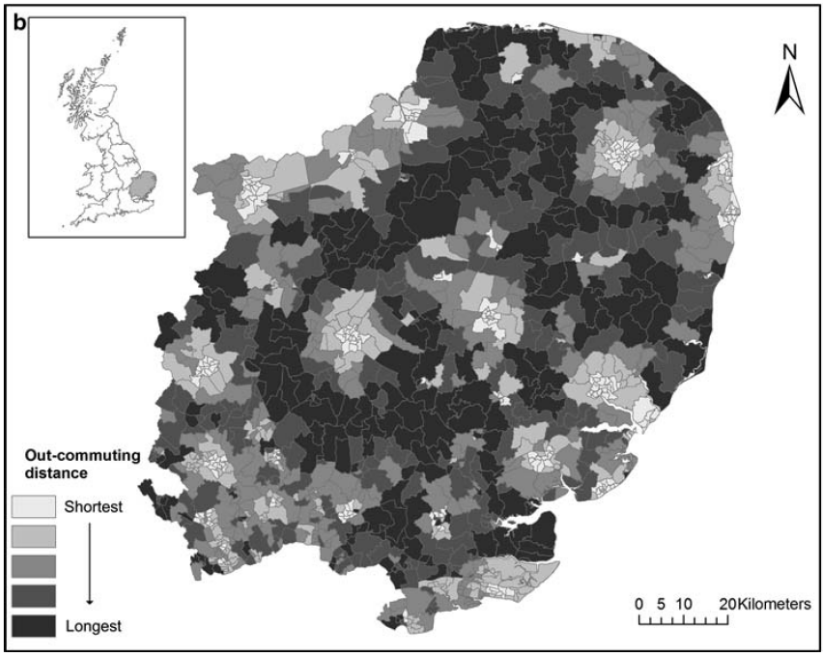
- Population-based case-control study of childhood leukemia
- Incident cases from 9 major pediatric clinical centers in N. & C. California
- Controls individually-matched (date of birth, sex, Hispanic status, and maternal race)
- Data collected through an in-home personal interview
- DNA from buccal cells or newborn blood spots



Validating Population Mixing Measures

Variation in commuting distance by ward (*Taylor JC et al., Eur J Epidemiology, 2008*)





- Areas with a higher median distance travelled by commuters leaving the area had a lower rate of hospital admissions for infections
- Deprived areas and densely populated areas had elevated rates of admissions

Total Child-hours Calculation

	No. other children	X	Months attended	X	Mean hrs/wk	X	4.35 wks/mo	=	Child-hours
1st	10		5		5		4.35		1,087.5
2nd	6		4		7		4.35		730.8
3rd	13		6		6		4.35		2,035.8

Total child-hours 3,854.1

Meta-Analysis: 14 Studies

Study, Year	Location	Disease	Age	Case/cont
Petridou et al., 1993	Greece	Leukemia	0-14	136/187
Roman et al., 1994	UK	ALL	0-4	38/112
Petridou et al., 1997	Greece	Leukemia	0-14	153/300
Schuz et al., 1999	Germany	AL, c-ALL	1.5-14	921/921
Dockerty et al., 1999	New Zealand	ALL	15 mo – 14	90/266
Infante-Rivard et al., 2000	Canada	ALL	0-9	433/416
Rosenbaum et al., 2000	USA	ALL	0-14	158/499
Neglia et al., 2000	USA	ALL, c-ALL	1-14	1744/1879
Chan et al., 2002	Hong Kong	AL, c-ALL	2-14	98/228
Perrillat et al., 2002	France	AL	2-15	246/237
Jourdan-Da Silva et al., 2004	France	AL, ALL	1-15	387/525
Gilham et al., 2005	UK	ALL, c-ALL	2-14	1272/6238
Ma et al., 2005 (NH-Whites)	USA	ALL, c-ALL	1-14	136/172
Ma et al., 2005 (Hispanics)	USA	ALL, c-ALL	1-14	120/153
Kamper-Jorgensen et al., 2008	Denmark	ALL, c-ALL	0-15	176/1571