To C or Not to C
That is the question !!

TARRANT Symposium 2011

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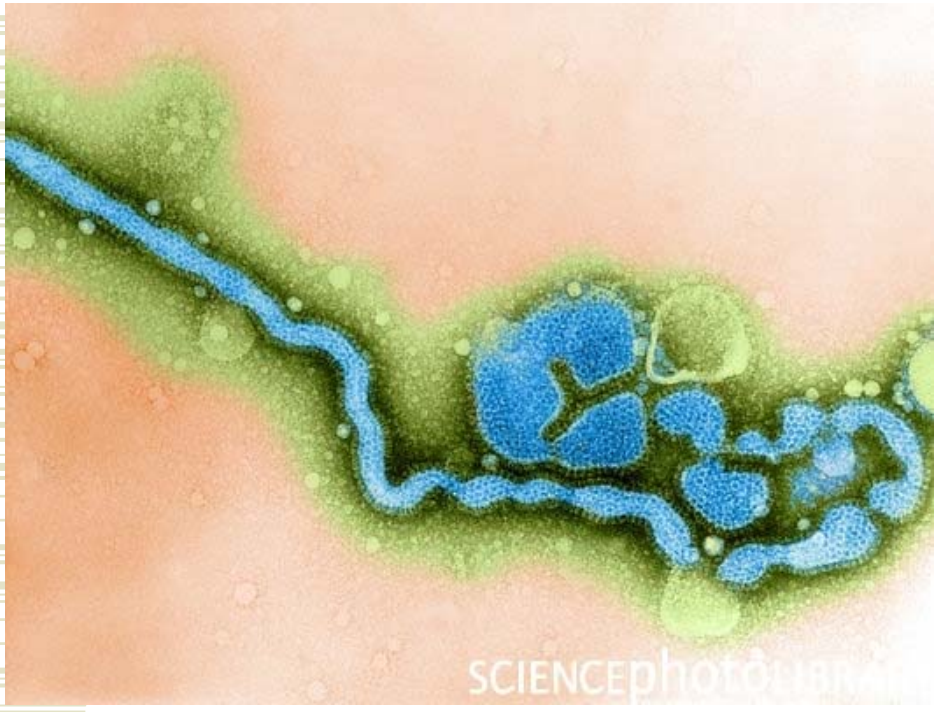

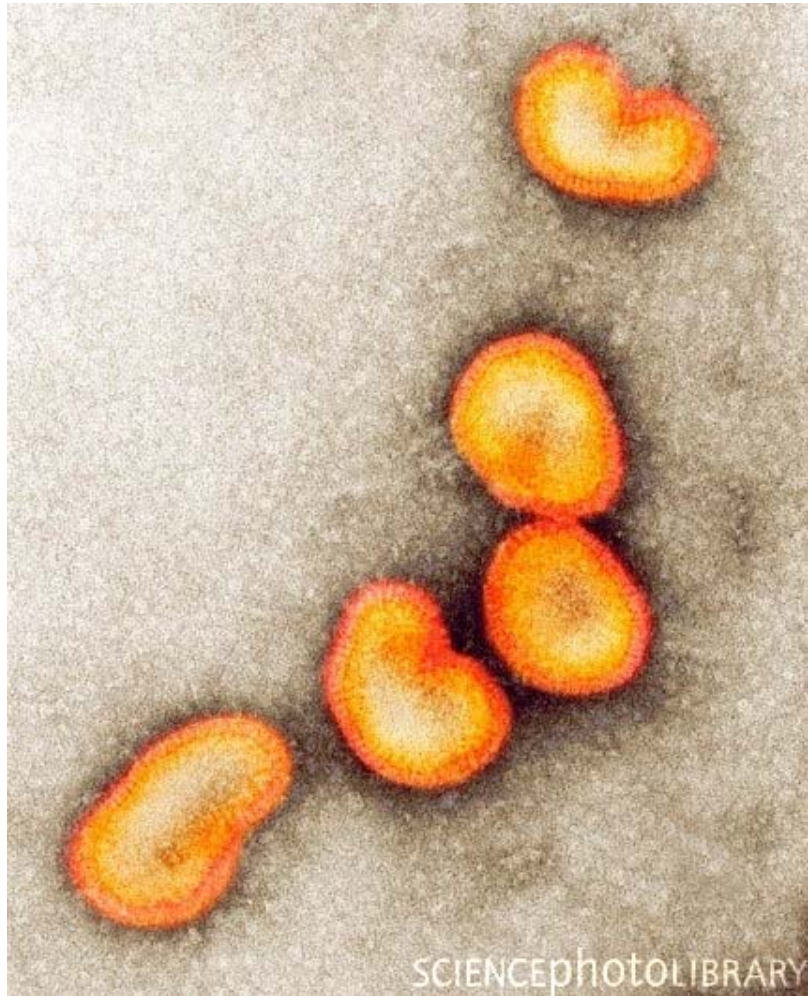

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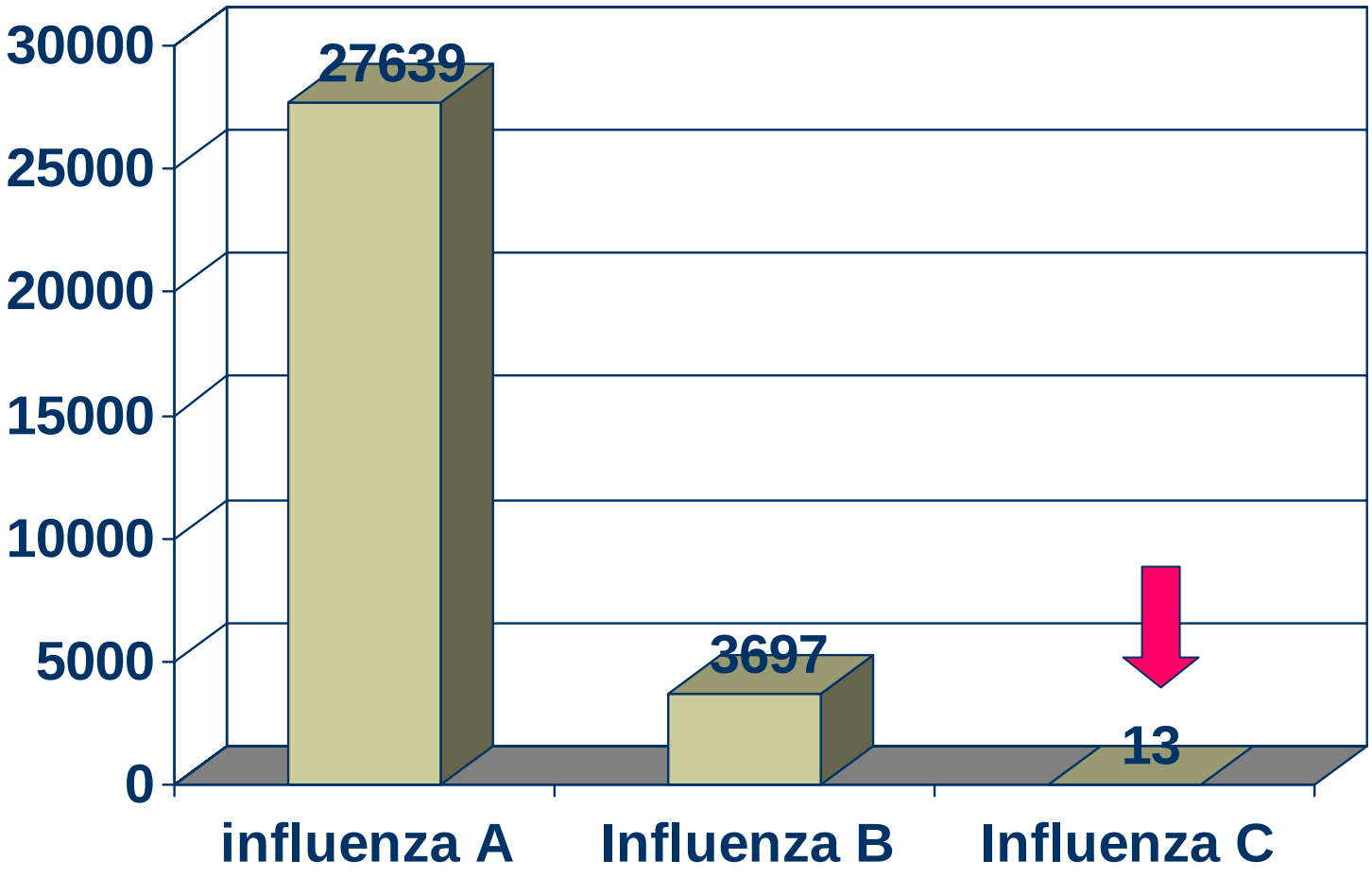
Literature – 2000 - 2011



No Canadian data for past 20+ years !!!

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Genetic data for Influenza C (data from Sallene Wong)

- Complete gene sequence of the 7 genes on C/Ann Arbor/1/50
- Almost complete data on C/Nara/2/85 & C/Nara/82
- Most recent entry is from France on C/Caen/BA1/2007
- For the other influenzas ……..TNTC

Temporal Association with Infection in Children

Table 1. Monthly isolation of influenza C virus between December 1990 and November 2004.

	Clinic		Hospital		Total	
Month of year	Total	Positive	Total	Positive	Total	Positive
January	4962	15 (0.30)	3306	3 (0.09)	8268	18 (0.22)
February	7117	22 (0.31)	4135	4 (0.10)	11,252	26 (0.23)
March	6225	26 (0.42)	3636	8 (0.22)	9861	34 (0.34)
April	3402	20 (0.59)	2574	8 (0.31)	5976	28 (0.47)
May	3332	20 (0.60)	2856	7 (0.25)	6188	27 (0.44)
June	3998	20 (0.50)	2958	11 (0.37)	6956	31 (0.45)
July	4666	6 (0.13)	2942	1 (0.03)	7608	7 (0.09)
August	2510	0	2212	1 (0.05)	4722	1 (0.02)
September	2825	2 (0.07)	2311	0	5136	2 (0.04)
October	3085	1 (0.03)	2429	2 (0.08)	5514	3 (0.05)
November	3499	0	2803	2 (0.07)	6302	2 (0.03)
December	3930	7 (0.18)	3233	1 (0.03)	7163	8 (0.11)
Total	49,551	139 (0.28)	35,395	48 (0.14)	84,946	187 (0.22)

NOTE. Data are no. (%) of specimens.

Matsuzaki et al JID 2006

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Influenza C & Hospitalization in Children

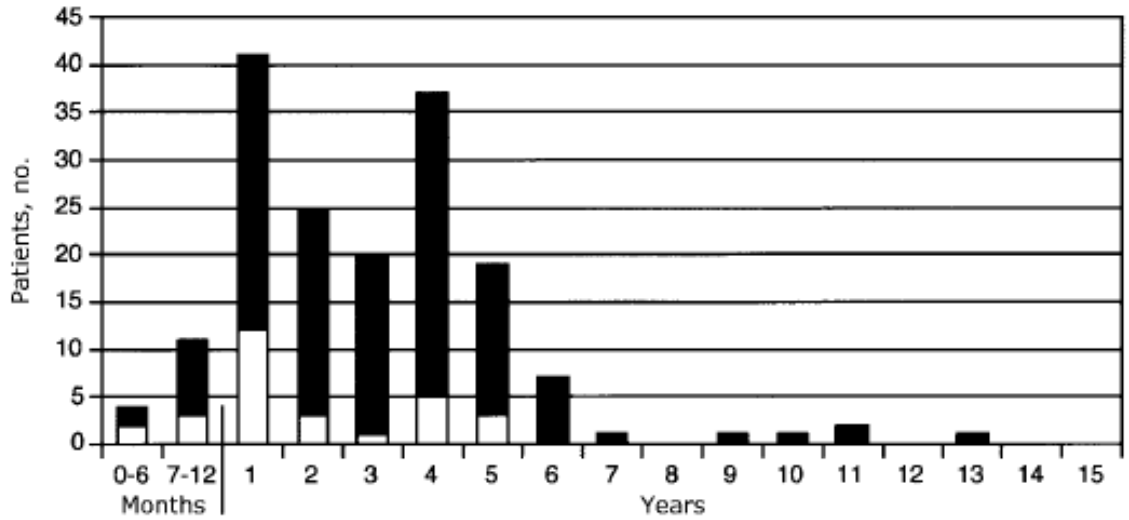

Figure 1. Age distribution of influenza C virus–infected children. Hospitalized children are represented by white bars.

Matsuzaki et al JID 2006

Table 2. Clinical diagnoses in influenza C virus–infected children.

Clinical diagnosis	Nonhospitalized children (n = 141)	Hospitalized children (n = 29)	Total (n = 170)
Upper-respiratory-tract illness	91 (64.5)	1 (3.4)	92 (54.1)
Influenza	20 (14.2)	0	20 (11.8)
Bronchitis	12 (8.5)	3 (10.3)	15 (8.8)
Pneumonia	2 (1.4)	15 (51.7)	17 (10.0)
Bronchiolitis	1 (0.7)	3 (10.3)	4 (2.4)
Asthma	2 (1.4)	1 (3.4)	3 (1.8)
Croup	7 (5.0)	2 (6.9)	9 (5.3)
Tonsillitis	0	1 (3.4)	1 (0.6)
Sinusitis	3 (2.1)	0	3 (1.8)
Otitis media	0	1 (3.4)	1 (0.6)
Gastroenteritis	2 (1.4)	0	2 (1.2)
Kawasaki disease	0	2 (6.9)	2 (1.2)
Henoch-Schoenlein purpura	1 (0.7)	0	1 (0.6)

NOTE. Data are no. (%) of children.

Influenza A or C infection ??

Table 4. Comparison of clinical features of type C and A influenza virus infections at Katsushima Pediatric Clinic during January–March 2002.

Characteristic or symptom	Type C influenza (n = 17)	Type A influenza (n = 63)
Age, mean ± SD, years	2.82 ± 1.38	2.70 ± 1.41
Fever[a]	13 (76.5)	63 (100)
Maximum temperature, mean ± SD, °C	38.38 ± 0.61	39.22 ± 0.56
Duration of fever, mean ± SD, days		
Not treated by anti-influenza drug	2.13 ± 1.19	5.06 ± 2.08
Treated by anti-influenza drug		2.75 ± 1.08
Cough	12 (70.6)	41 (65.1)
Rhinorrhea	10 (58.8)	19 (30.2)
Wheeze	0	1 (1.6)
Vomiting	0	6 (9.5)
Diarrhea	1 (5.9)	4 (6.3)
Abdominal pain	1 (5.9)	3 (4.8)
Exanthema	0	3 (4.8)
Conjunctivitis	0	1 (1.6)

NOTE. Data are no. (%) of children, unless otherwise indicated.

[a] Temperature >38°C.

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Influenza C infection in Adults

- 200 patients with ILI (Oct 1994 – Nov 1995)
  - Mean age 24 years
  - Males 59, Females 141
  - Combination of serology & molecular tests

Table 2. Laboratory and clinical findings for 8 study participants with evidence of acute or recent influenza C infection.

Patient	Age[a]/sex	Onset of common cold	RT-PCR		Antibody titer		Fever ≥37.5°C	Duration of fever, days	Radiologically confirmed sinusitis[d]	Duration of illness, days
			Day 0	Day 7	Acute[b]	Convalescent[c]				
24	22/F	December 1994	+	−	800	102,400	Yes	1	Yes	12
60	25/F	February 1995	+	−	3200	25,600	No		No	14
67	25/F	February 1995	+	−	1600	25,600	Yes	1	Yes	14
98	23/F	March 1995	+	−	400	12,800	No		No	12
111	24/M	March 1995	+	−	1600	25,600	No		No	9
118	22/F	April 1995	+	−	1600	25,600	No		No	12
160	20/F	May 1995	−	−	25,600	204,800	No		Yes	16
162	21/F	May 1995	+	+	3200	25,600	Yes	2	Yes	19

NOTE. RT-PCR, reverse transcription–polymerase chain reaction; +, positive; −, negative.

[a] Age in years at study entry.

[b] Serum sample obtained at study entry.

[c] Serum sample obtained at second control visit on day 21.

[d] Plain radiography of the paranasal sinuses (occipitomental view) was carried out on days 1, 7, and 21 of illness. Maxillary sinusitis was established radiologically by the presence of mucosal thickening >5 mm, total opacity or air-fluid level.

Hirsila et al JID 2001

Serological Data

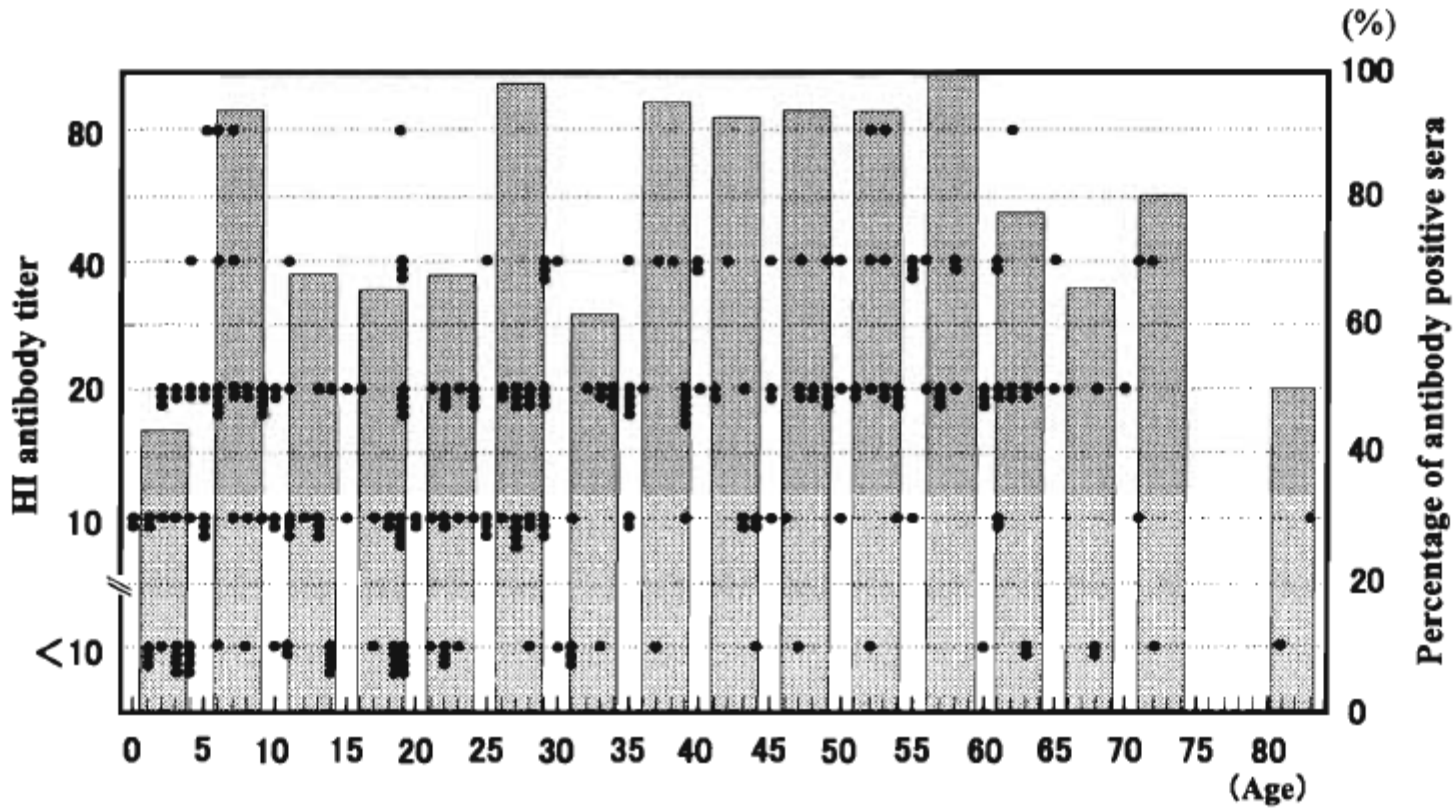
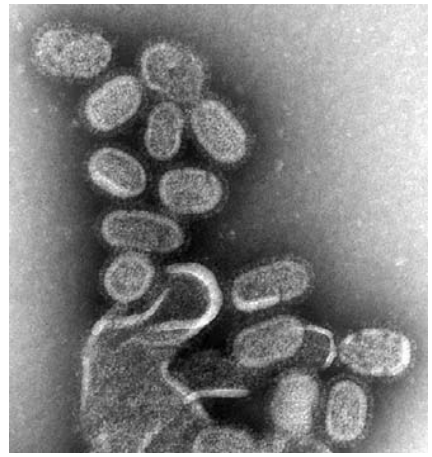


Fig. 1. Age-related distribution of antibody and antibody-positive rate in age groups against influenza C virus. Hemagglutination-inhibition (HI) titers of 186 sera collected from residents of Hiroshima Prefecture in 1997 were determined using the microplate technique described by Homma (3). The antigen for HI test was the isolate of influenza C virus (C/Hiroshima/290/99) (5). HI titers were expressed as the reciprocal of highest serum dilution that inhibited hemagglutination, and were plotted against age. The percentages of antibody-positive sera (HI titer of 1:10 or more) were determined every 5 years of age, and are shown as bars on the graph.

Takao et al Lab Epi Comm 2001

The Influenza viruses



	Influenza A	Influenza B	Influenza C
Genome	8 genes	8 genes	7 genes
Variants	Subtypes	Lineages	Antigenic groups
Genetic expansion	Reassortment & Recombination	Reassortment & Recombination	Reassortment
Hosts	Avian, human, animals	Human, seals (dogs)	Human, swine
Disease	Pandemics & outbreaks	Outbreaks	Sporadic (outbreaks)
Clinical	Mild to severe	“mild to less severe”	“mild”

Influenza C Basic Biology

Segment	Gene	Function
1	PB2	Polymerase subunit PB2
2	PB1	Polymerase subunit PB1
3	PB3	RNA polymerase
4	HEF	Haemagglutinin-esterase-fusion protein
5	NP	Nucleoprotein
6	M	Matrix protein
7	NS1	Nonstructural protein 1

Segment	Size	Peptide(s)	Function
1	2341	PB2	RNA polymerase subunit
2	2341	PB1	RNA polymerase subunit
3	2233	PA	RNA polymerase
4	1778	HA	Haemagglutinin
5	1565	NP	Nucleoprotein
6	1413	NA	Neuraminidase: release of virus
7	1027	M1	Matrix protein: major component of virion
		M2	Integral membrane protein - ion channel
8	890	NS1	Anti-interferon protein/virulence factor.
		NS2	“Virulence factor”

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Antigenic groups of Influenza C

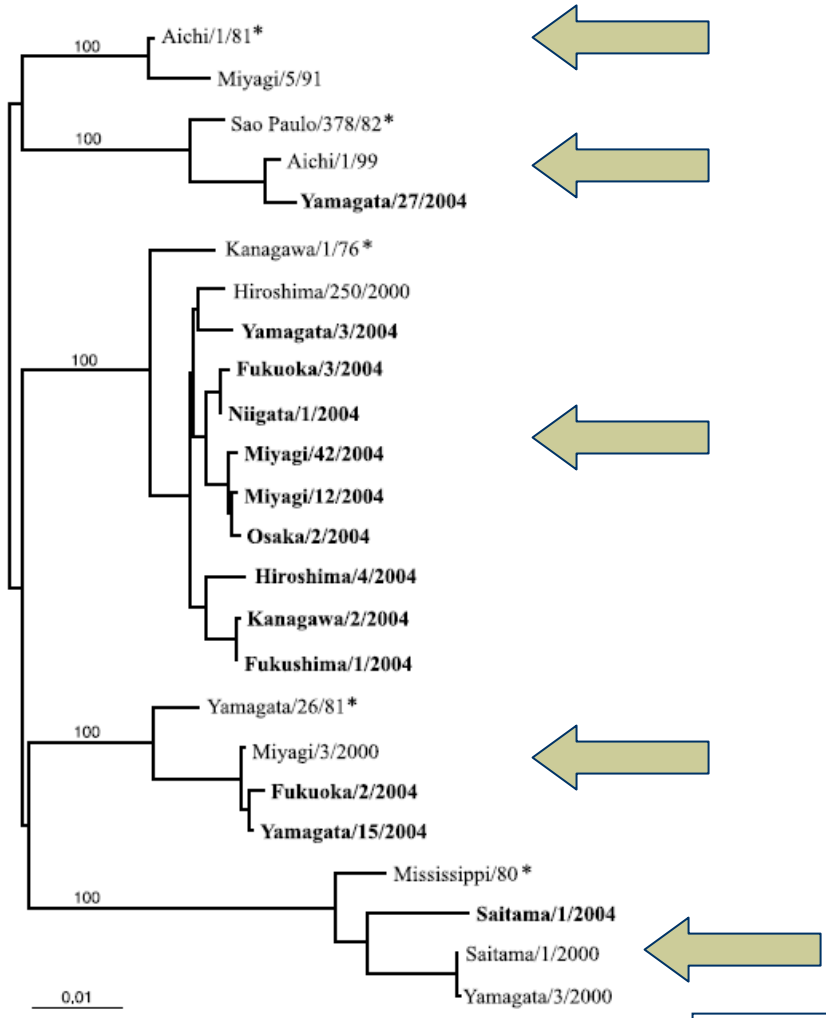

FIG. 2. Phylogenetic tree for the influenza C virus based on the coding region from nucleotide 64 to 1989 of the HE gene. Representative strains of the HE gene lineage are marked by asterisks. Viruses isolated in the present study are indicated in boldface. Numbers above the branches are the percent bootstrap probabilities of each branch determined by the PHYLIP program (version 3.573c).

Matsuzaki et al JCM 2007

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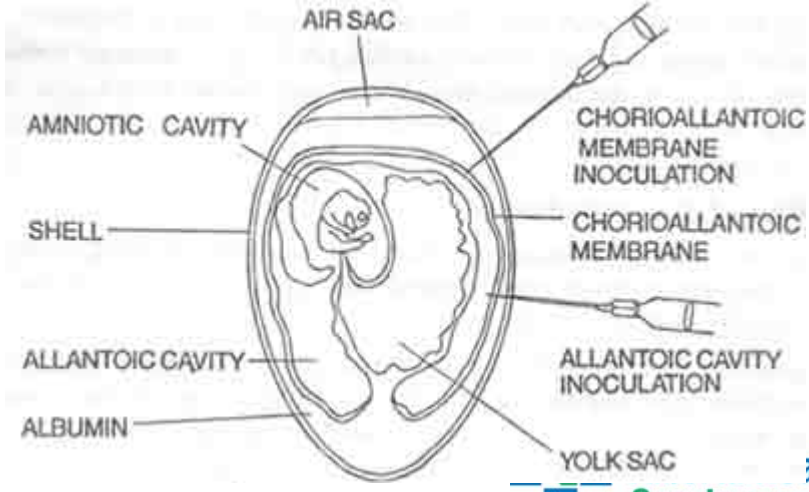
Why do we not see more C ?

- Lack of interest – even in text books (Fields Virology)
- Virus is notoriously difficult to grow in cell lines
  - No obvious CPE
  - Needs a shell vial approach to culture
  - Best technique is embryonated eggs
- Serology – acute & convalescent sera; not helpful on single samples



The Plan

- Year 1: Develop and validate assay
  - Selection of samples (500 in total)
    - negative for the current panel of respiratory viruses,
    - from children $\leq$ 10 years old,
    - taken at a hospital (agency designation =hospital) and
    - collected between September 1, 2010 and April 30, 2011.
- Year 2: apply to a wider sample type
  - ? TARRANT samples
- Year 3: incorporate into respiratory algorithm

Outcomes & Questions

- Assemble some Real Canadian data
- Define the patient population affected
- Role in outbreaks
- Association with hospitalizations
- Seasonality ?
- ? Antiviral resistance
- Grow up the virus !!
- Genotype studies
- Seroprevalence

Cing' is Believin'

Questions ?

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