Genetic variation at the *IFITM3* and Influenza A(H1N1)pdm09 infection severity in the Portuguese population

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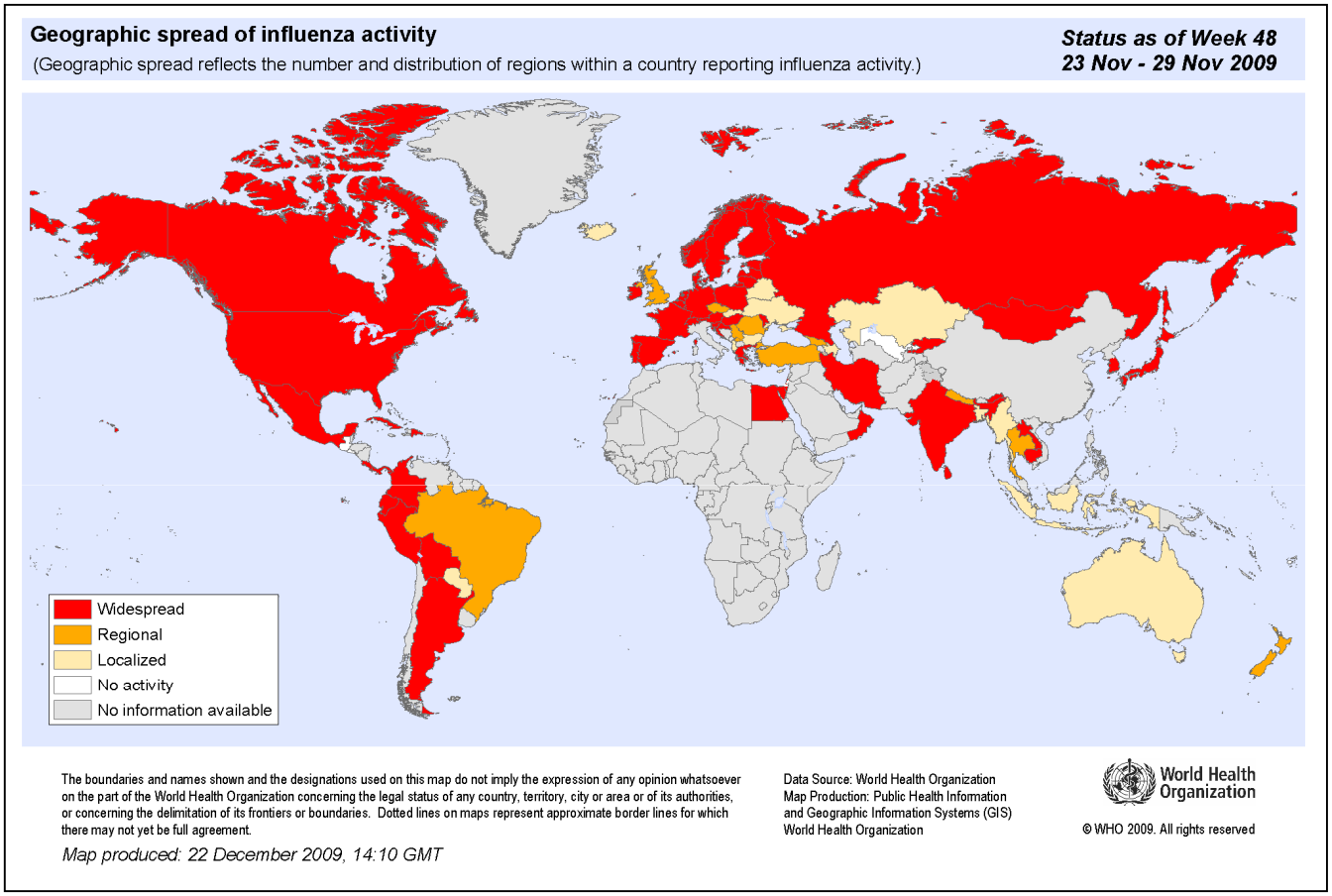
1.Background



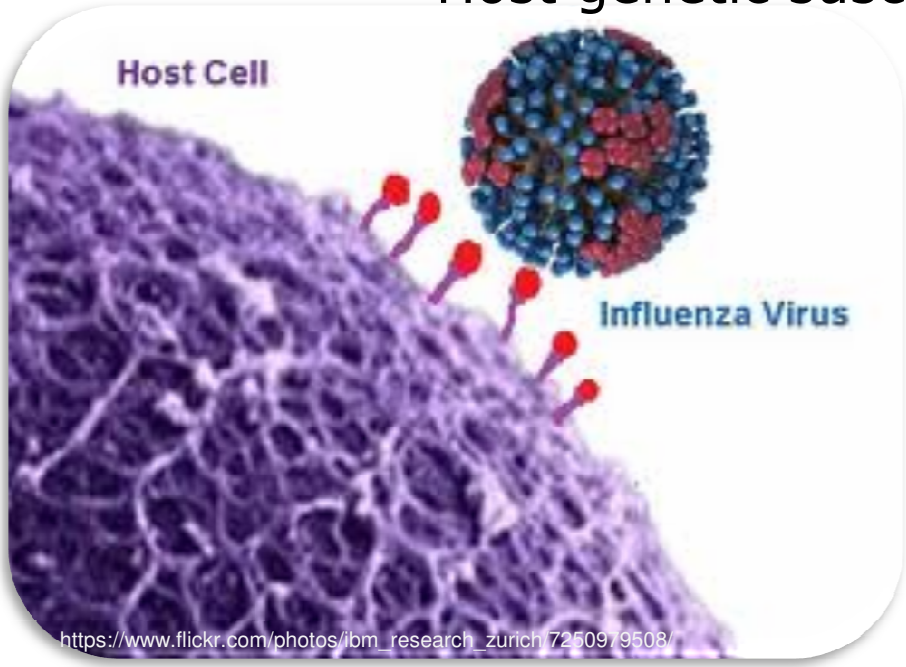
Influenza A(H1N1)pdm09

15,000 deaths in less than a year
Healthy young people

1. Background

Why do some individuals resist to infection or recover quickly, whereas others experience severe disease associated with the infection?

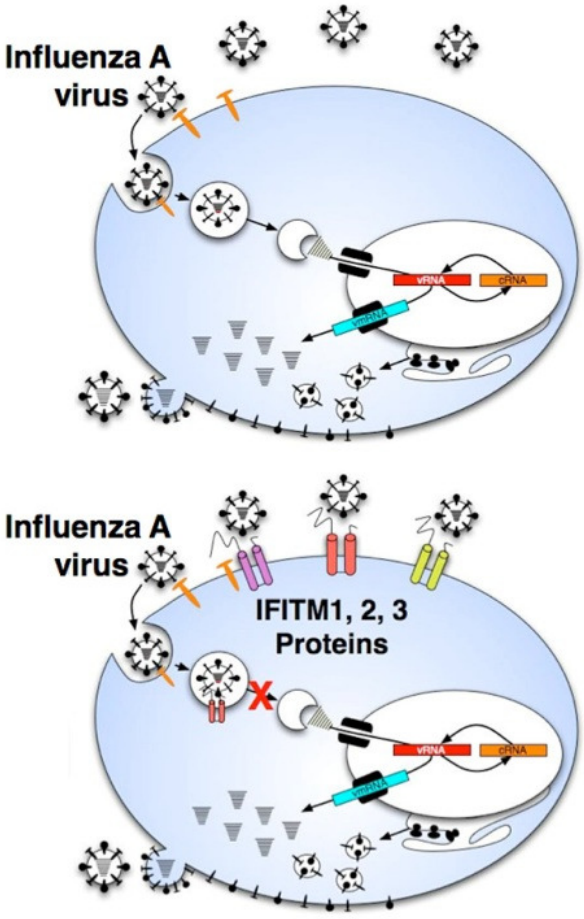
- Virus pathogenicity } Intensive research
- Host genetic susceptibility } **?**



https://www.flickr.com/photos/ibm_research_zurich/72509/9508/

WHO (2009):
identified studies of the host genetic factors' role on susceptibility to severe influenza as a priority.

1. Background



LETTER Everitt *et al,* 2012

doi:10.1038/nature10921

IFITM3 restricts the morbidity and mortality associated with influenza

Aaron R. Everitt[1], Simon Clare[1], Thomas Pertel[2], Sinu P. John[2], Rachael S. Wash[1], Sarah E. Smith[1], Christopher R. Chin[2], Eric M. Feeley[2], Jennifer S. Sims[2], David J. Adams[1], Helen M. Wise[3], Leanne Kane[1], David Goulding[1], Paul Digard[3], Verneri Anttila[1], J. Kenneth Baillie[4,5], Tim S. Walsh[5], David A. Hume[4], Aarno Palotie[1], Yali Xue[1], Vincenza Colonna[1,6], Chris Tyler-Smith[1], Jake Dunning[7], Stephen B. Gordon[8], The GenISIS Investigators*, The MOSAIC Investigators*, Rosalind L. Smyth[9], Peter J. Openshaw[7], Gordon Dougan[1], Abraham L. Brass[2,10] & Paul Kellam[1,11]

- *IFITM3* alters the course of influenza virus infection;

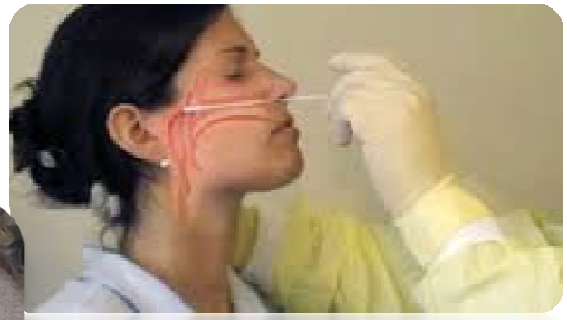
- Association between a minor *IFITM3* allele (SNP rs12252-C) and severity of the disease.

2. Research question

Is C allele of the *IFITM3* rs12252 associated with susceptibility and/or severity to Influenza A(H1N1)pdm09 infection in the Portuguese population?

3. Methods

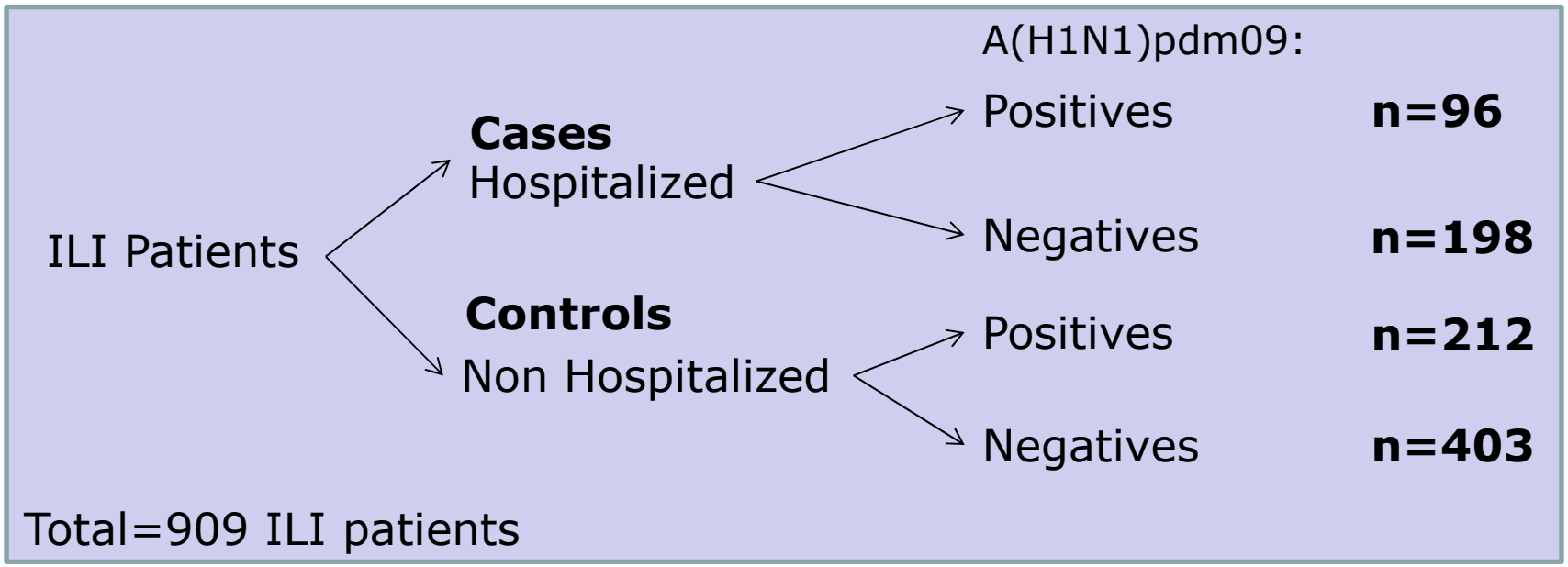
- Case-Control Study;
- Database of the Portuguese Laboratory Network for the Diagnosis of Influenza Infection (Only samples available in the National Health Institute);
- Nasal swabs from patients with Influenza-like illness (ILI);



Exclusion Criteria:

- Samples available in other Portuguese laboratories;
- Pregnant women, chronic patients, immunodepressed or transplanted patients;
- Age >65 years;
- Disease onset before 01/09/2009
- >7 days between the initial symptoms and the sample collection.

Cases and controls selection (2 paired controls : 1 case)



Genotyping:

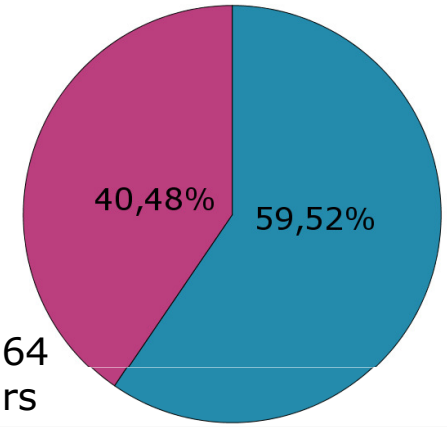
- DNA extraction (MagNA Pure LC – Roche);
- SNP rs12252 genotyped by RFLPs;

4. Results

Patients Characterization

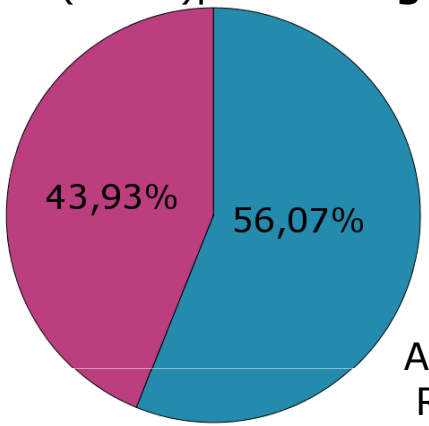
male
female

Cases
Hospitalized
A(H1N1)pdm09 **Positives**



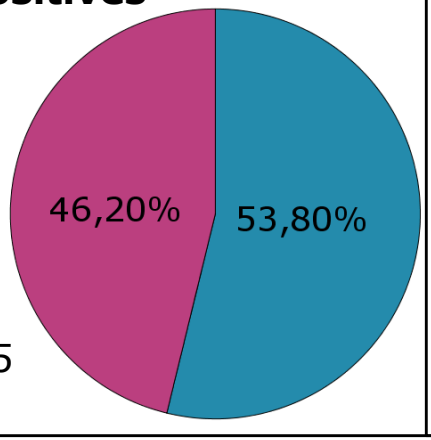
Average Age:16,64
Range: 0-60 years

Cases
Hospitalized
A(H1N1)pdm09 **Negatives**



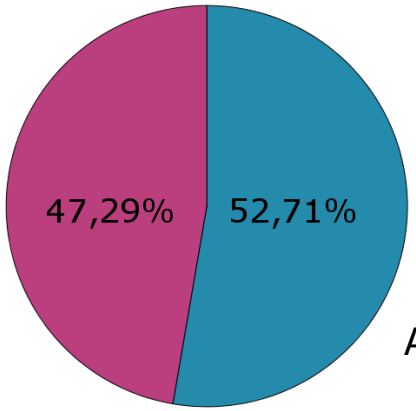
Average Age:15,69
Range: 0-64 years

Controls
Non Hospitalized
A(H1N1)pdm09 **Positives**



Average Age:13,95
Range:0-54 years

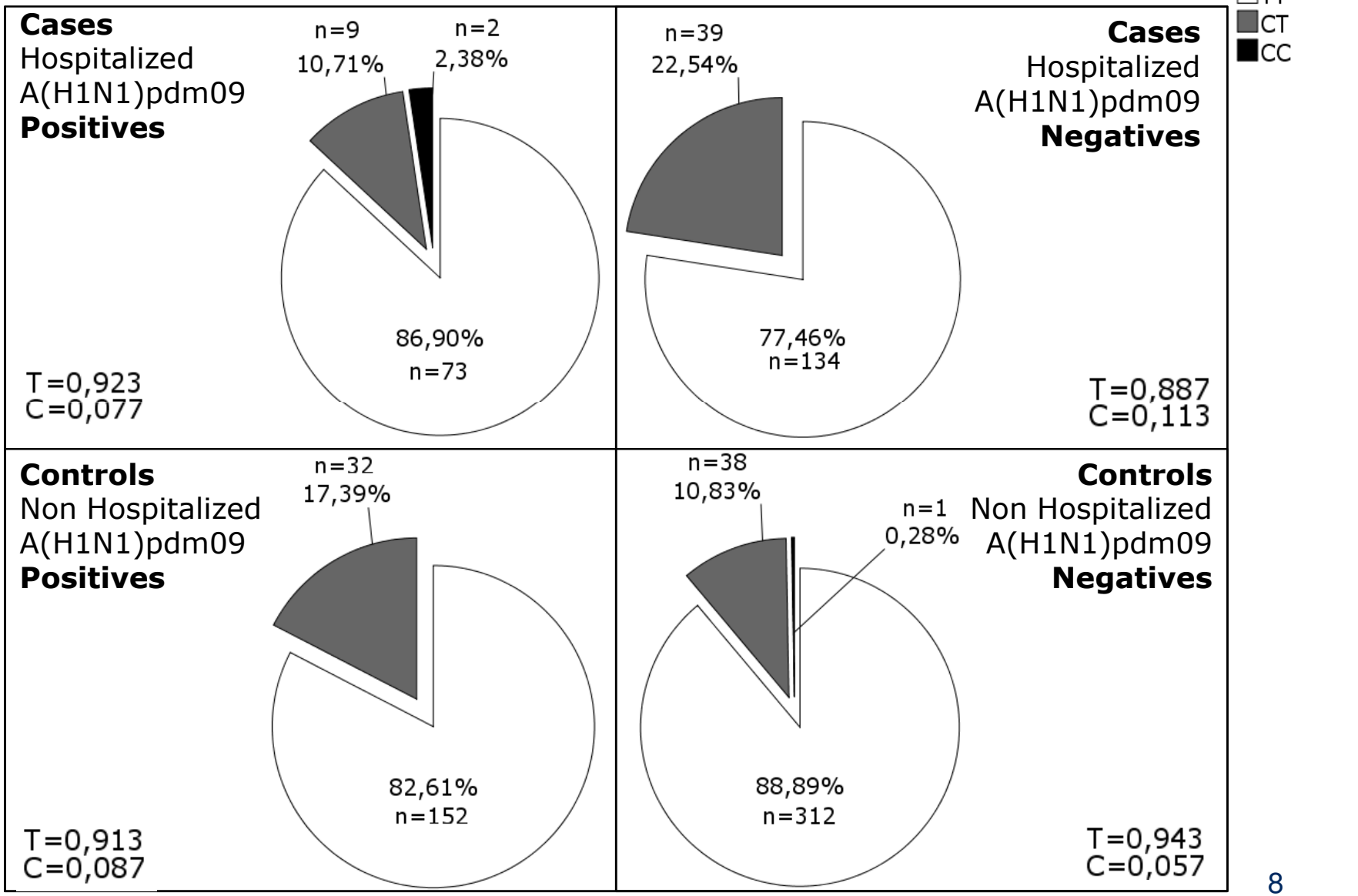
Controls
Non Hospitalized
A(H1N1)pdm09 **Negatives**



Average Age:13,52
Range:0-62 years

4. Results

Genotypic Frequencies



Stratified analysis I

			Hospitalization		
			Hospitalized **(Cases)**	Non Hospitalized **(Controls)**	
Influenza A(H1N1)pdm09	Positive	CT/CC	11	32	**Stratum 1**
		TT	73	152	
	Negative	CT/CC	39	39	**Stratum 2**
		TT	134	312	

Stratum 1 - Is there a higher risk of being hospitalized for C allele carriers in the case of Influenza A(H1N1)pdm09 infection?

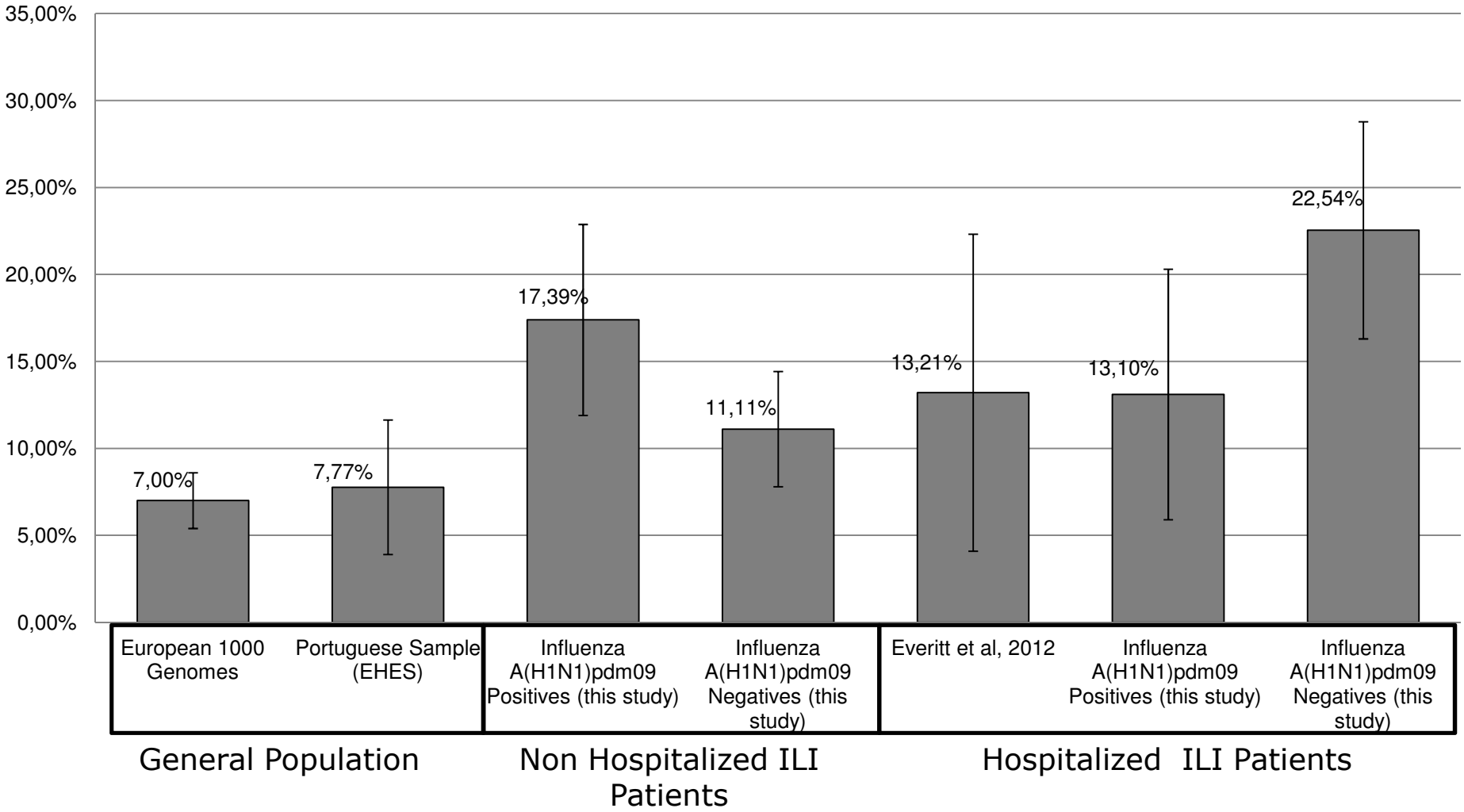
Odds Ratio: 0.72 (95%CI: 0.34- 1.50)
*Adjusted Odds Ratio: 0.73 (95%CI: 0.35-1.53)

Stratum 2 - Is there a higher risk of being hospitalized for the C allele carriers in the case of no Influenza A(H1N1)pdm09 infection?

Odds Ratio: 2.33 (95%CI: 1.43- 3.79)
*Adjusted Odds Ratio: 2.54 (95%CI: 1.54-4.18)

* Adjustment for age and gender by logistic regression

C allele Carriers * - Comparison between populations



*One or two copies of the C allele in the *IFITM3* rs12252

5. Conclusions and Future Prespectives:

Is C allele of the *IFITM3* rs12252 associated with susceptibility and/or severity to Influenza A(H1N1)pdm09 infection in the Portuguese population?

✓ We observed that C allele was not associated with the susceptibility and/or severity to Influenza A(H1N1)pdm09 infection.

✓ We observed that C allele was associated with the severity of influenza-like illness in the case of no Influenza A(H1N1)pdm09 infection

5. Conclusions and Future Perspectives

• Hospitalization = good measure of the infection severity?
Less severe cases might have been hospitalized due to the initial pandemic alert.

• Detection of other respiratory virus in the Hospitalized Influenza A(H1N1)pdm09 negative samples.

Evidence of the IFITM3 role in resistance mediation to other virus infections (Brass et al, 2009).

• Sample size limitation due to the low C allele frequency.

• Future integrative approach of the genetic susceptibility to Influenza A(H1N1)pdm09 infection (virus-host genomes interactions, immunity, vaccination, weather conditions, etc).

Thank you for your attention!

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