

Le virus pandémique A/H1N1: l'expérience canadienne

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**Titulaire de la chaire de recherche du Canada sur les virus
émergents et la résistance aux antiviraux**

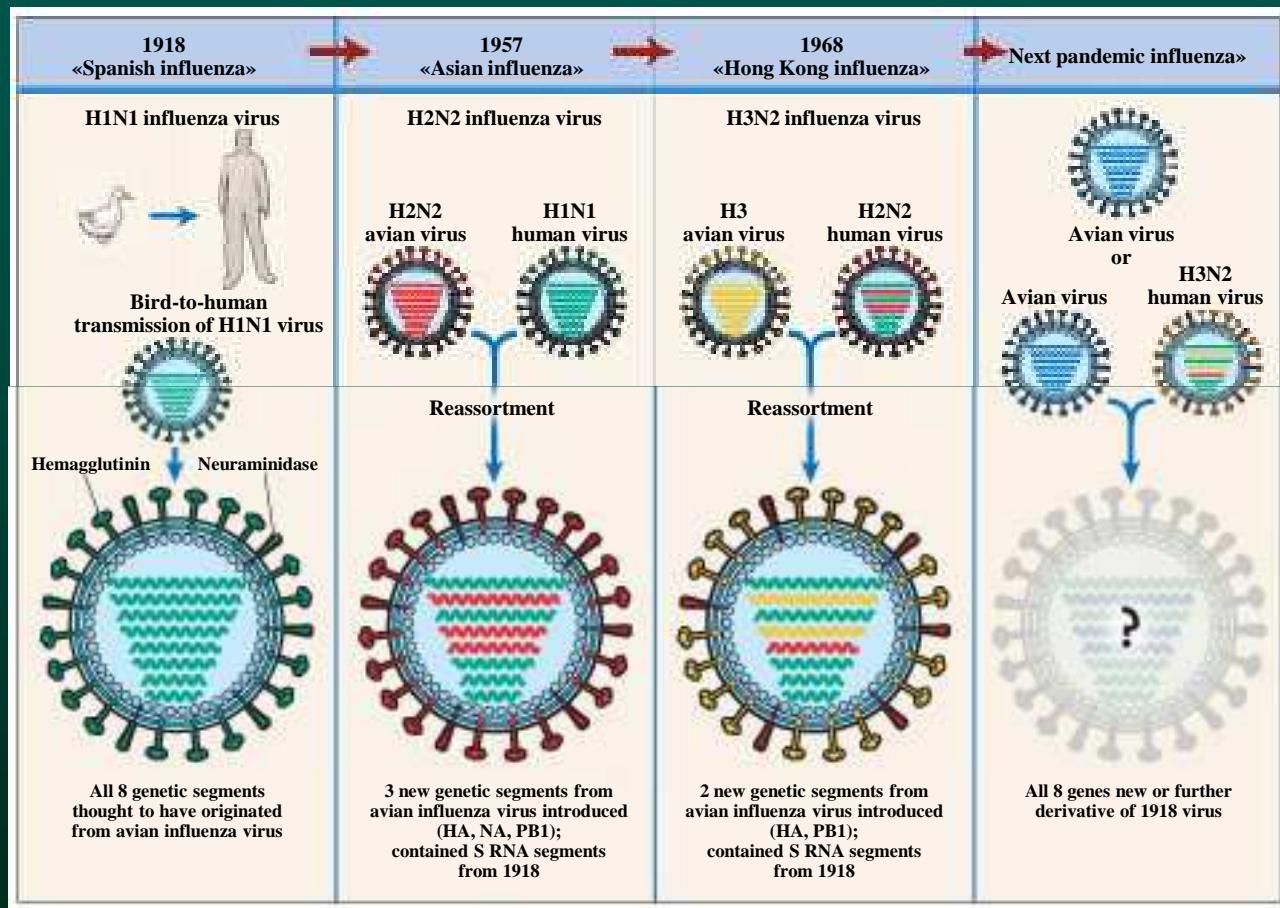


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Mécanismes à l'origine des pandémies d'influenza



N Engl J Med, November 24, 2005, 2209-11

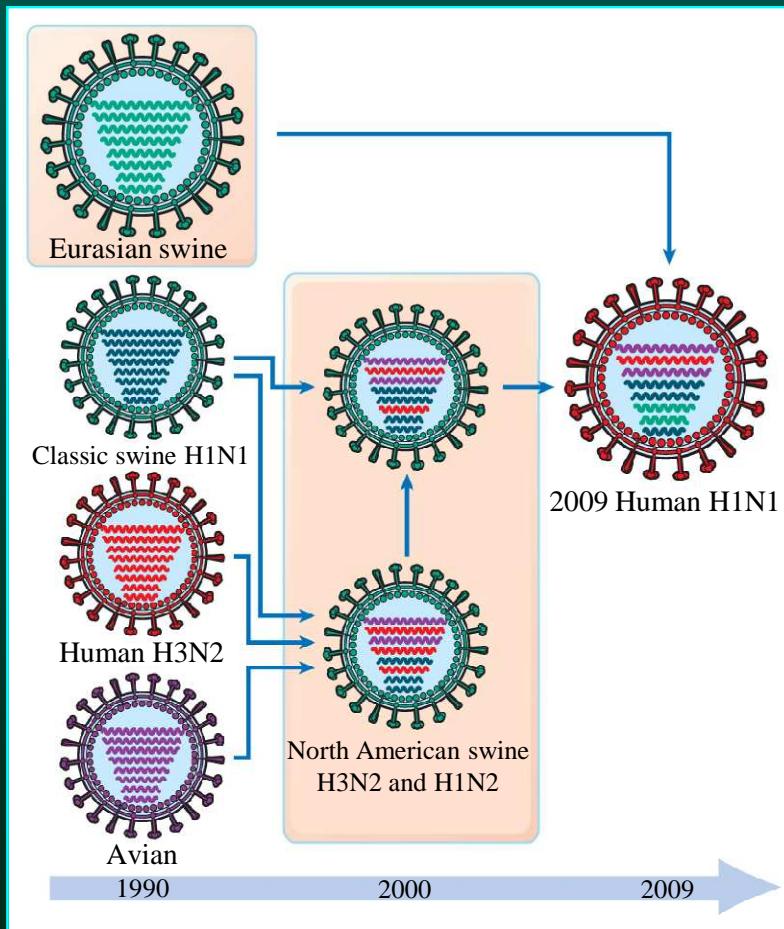


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Evolution des réassortiments du virus influenza A (H1N1) en 2009



The eight segments shown within each virus code for the following proteins of the influenza A virus (top to bottom): polymerase PB2, polymerase PB1, polymerase PA, hemagglutinin, nuclear protein, neuraminidase, matrix proteins, and nonstructural proteins. The segments of the human 2009 influenza A (H1N1) virus have coexisted in swine influenza A virus strains for more than 10 years. The ancestors of neuraminidase have not been observed for almost 20 years. The mixing vessel for the current reassortment is likely to be a swine host but remains unknown.

NEJM 2009; 361:115



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Taux d'hospitalisation et de mortalité au Canada

	Hospital admission	ICU admission	Deaths
1 st wave (May-July 09)	1488	292	78
2 nd wave (Oct.-Dec. 09)	7108	1154	348
Total	8596	1446	426

Official pandemic period: June 11 2009 to August 10 2010



Cas sévères (USI) au Canada

(N = 168 cas de 38 USI adulte/pédiatrique)

- Mean age : 32.3 yrs (\pm 21.4) including 30% children and 25% first nations
- Sex : 67.3% = females
- Co-morbidities : 98% (only 30% major)
- Duration of symptoms : onset → hospital (4 d) → ICU (1 d)
- Bacterial superinfection : 24% (staph > pneumoc.)
- Shock, ARDS, multi-organ failure
- 90 d mortality : 17.3%

* Kumar et al., JAMA 2009



Etude Québécoise cas-témoin sur les facteurs de risque pour l'hospitalisation et la maladie sévère

- Risk factors for hospitalization: age <5 yrs, underlying diseases, late consultation (≥ 5 d)
- Risk factors for severe dis. (ICU/death): female, underlying disease (cardiac, diabetes, pulmonary, neuro-muscular conditions)

Note: early antiviral use (≤ 3 d) decreases risk

* Gilca et al., submitted



Etude Québécoise familiale sur le pH1N1

- All family contacts of an index case prospectively tested
- NPA were tested by RT-PCR for pH1N1 and influenza A (days 1, 8 and 11)
- Sera (acute and convalescent) tested by MN and HAI:
seroconversion = titer $\geq 1:40$ or 4-fold increase in titers



Etude Québécoise familiale sur la contagiosité

- On day 8 : 74% PCR+, 19% culture+
(minimum 8% if all symptomatic PCR - patients are considered)
 - On day 11 : No positive culture
88% of retested patients still PCR+
- Thus, better to isolate for one week instead of using end of fever

De Serres et al., EID 2010



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Etude Québécoise familiale sur la transmission

- 43 index cases and 119 contacts recruited
- SAR = 45% (58% had FLI, 9.4% were asymptomatic, 2% had GI symptoms only)
- 81% of families had ≥ 1 confirmed contact case
- Mean serial interval = 3 days (median: 3.9 days)
- Young children (<7 yrs) had highest SAR
- GI symptoms (diarrhea, vomiting) were associated with increased transmission rate of pH1N1

Papenburg et al., CID 2010



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Thérapie antivirale pour les infections à pH1N1

- Virus is almost always resistant to amantadine and rimantadine
- Therapy with NAIs (oseltamivir or zanamivir) is required for patients with underlying risk factors including pregnancy and those with severe disease
- For severe cases (in ICU), consider higher doses (150 mg BID) and prolonged duration (up to 10 days) of oseltamivir
- For severe cases, treatment is warranted even when delayed after 48h
- For patients with suspected oseltamivir resistance, start inhaled zanamivir or IV zanamivir (if available) for severe cases
- Focus is on early treatment instead of PEP to decrease resistance

NEJM 2010, WHO committee



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Les virus pH1N1 résistants à l'oseltamivir (OMS- 27 octobre 2010-)

- **313 resistant viruses reported (1% of those tested)**
- All but one had at least H275Y NA mutation (one had I223R)
- All were susceptible to zanamivir but cross-resistant to peramivir
- Risk groups : Immunocompromised (30%), treated immunocompetent (32%), PEP (6%), no treatment (10%), preliminary info (22%)
- Limited clusters of resistant strains, sometimes without antiviral use



Symptômes, traitement antiviral et résultats virologiques du cas index (fils) et du cas contact (père)

Date (2009)	06-24	06-25	06-26	06-27	06-28	06-29	06-30	07-01	07-02	07-03	07-04	07-05	07-06	07-07	07-08	07-09	07-10
Symptoms																	
Son																	
Father																	
Treatment with Oseltamivir																	
Son																	
Prophylaxis with Oseltamivir																	
Father																	
PCR Influenza A/H1N1																	
Son						(+)											
Father																(-)	
Culture of Influenza A/H1N1						(+)						(+)					
Son																	
Father																	ND
Phenotype of susceptibility to oseltamivir																	
Son																	
Father																	ND
Presence of H275Y mutation																	
Son						(-)											
Father																NA	

(+) = Positive; (-) = Negative; (S) = Susceptible; (R) = Resistant; ND = Not done; NA = Not applicable

Baz et al., NEJM 2009



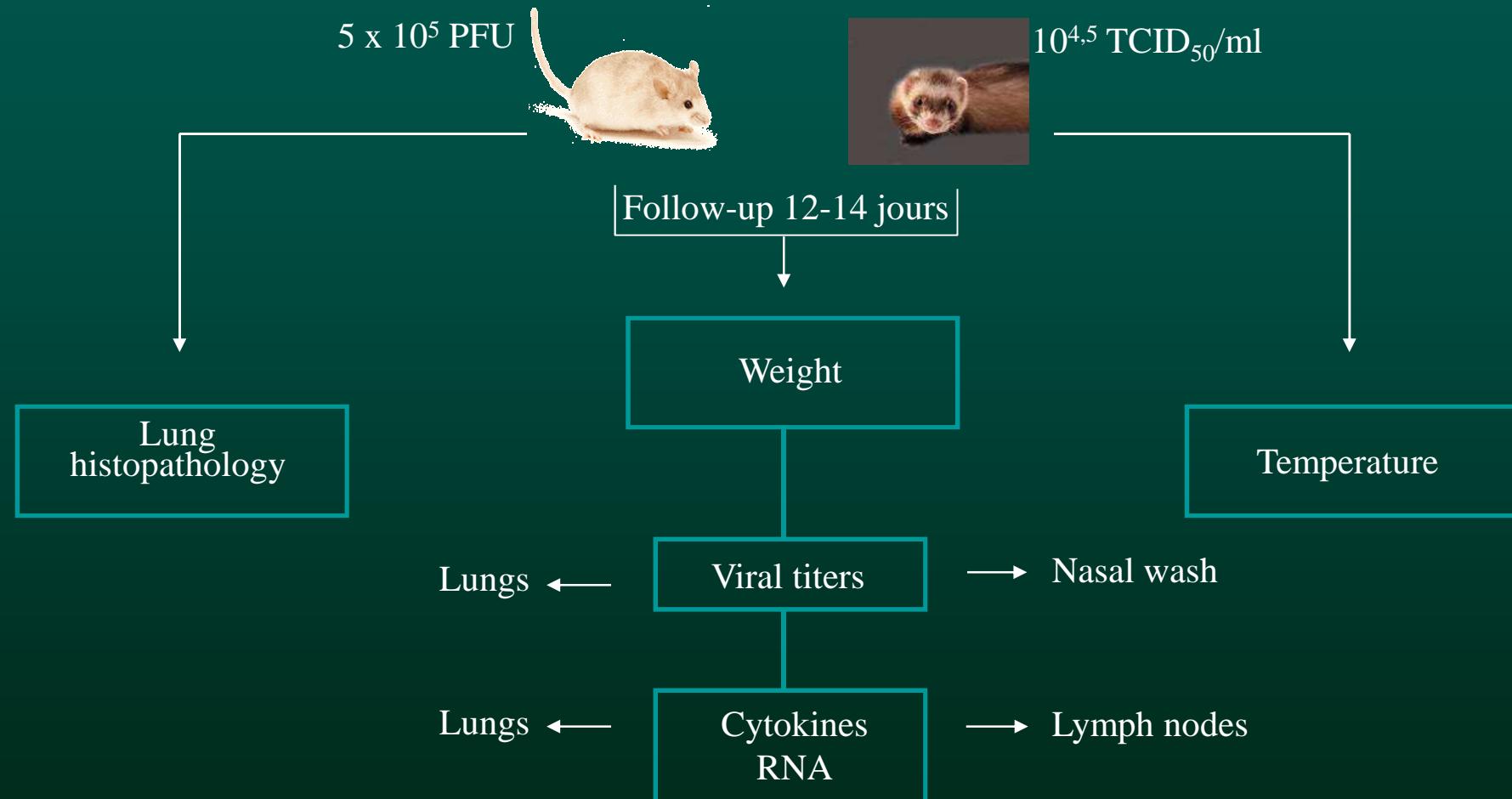
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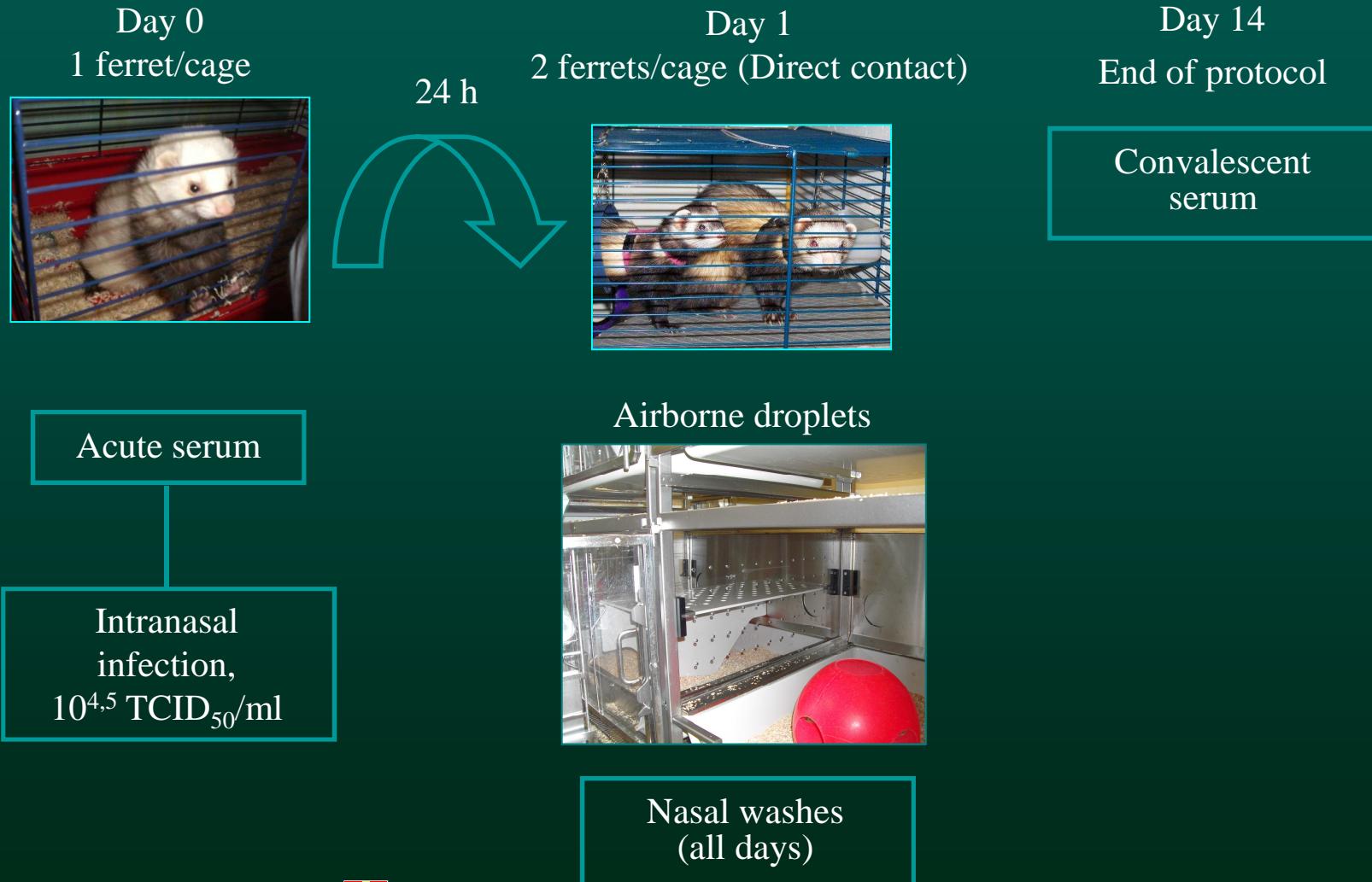
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Virulence chez la souris Balb/C et le furet

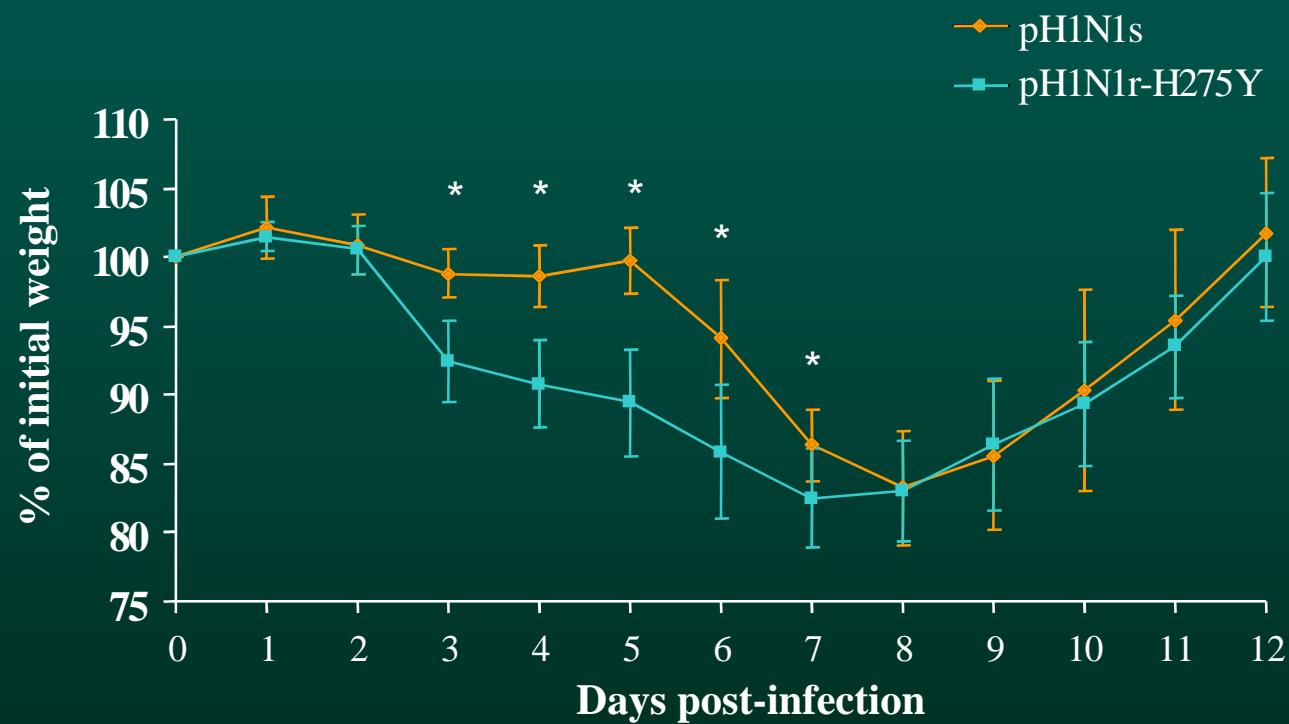
Intranasal infection (WT and H275Y mutant)



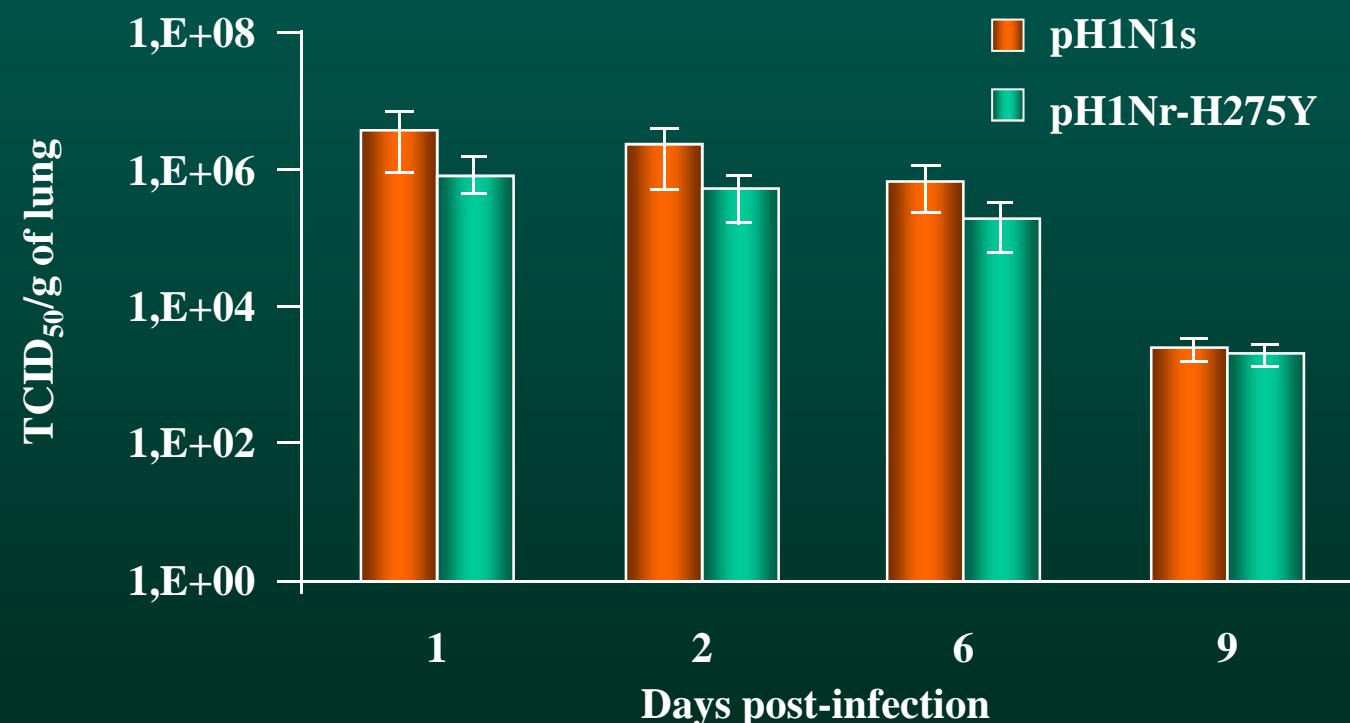
Transmission chez le furet



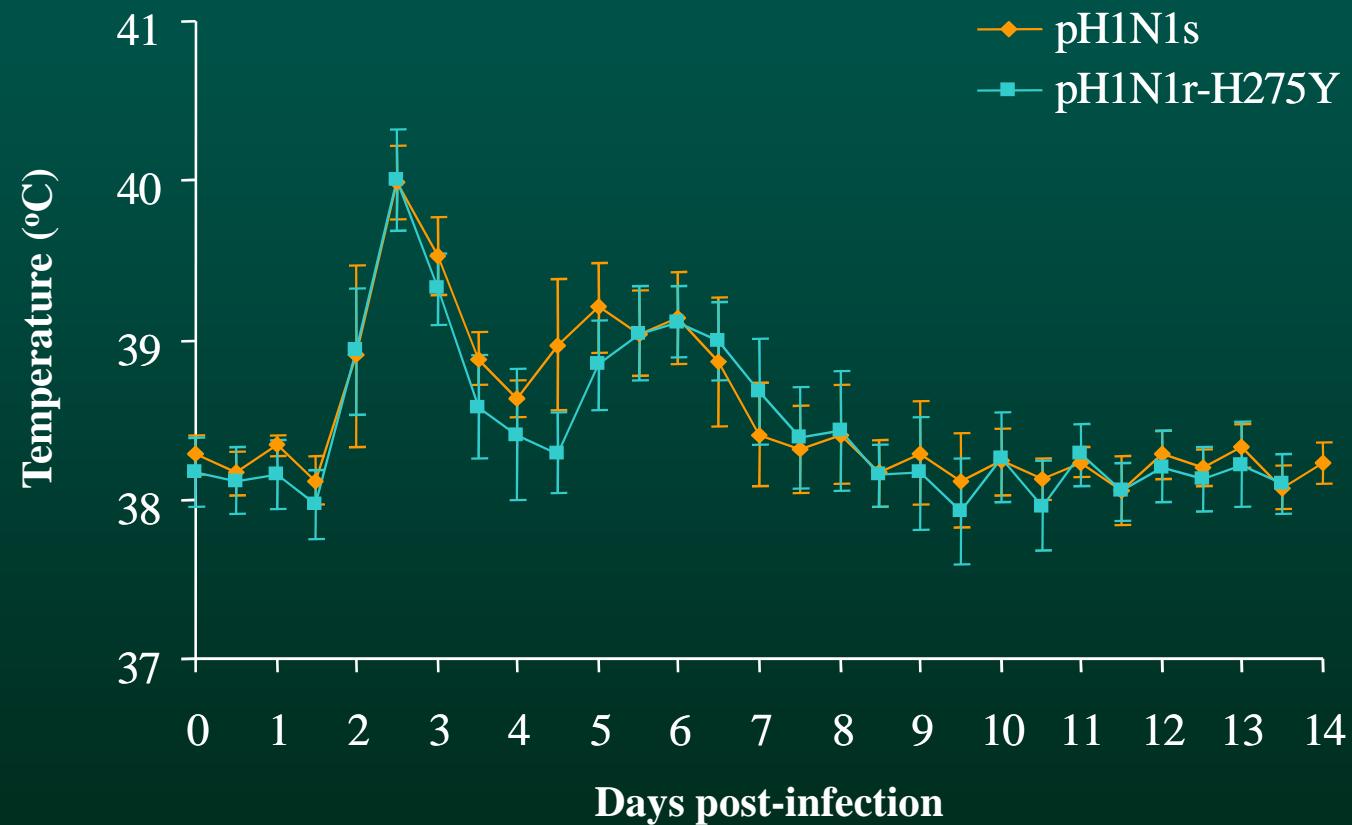
Perte de poids post-infection chez la souris



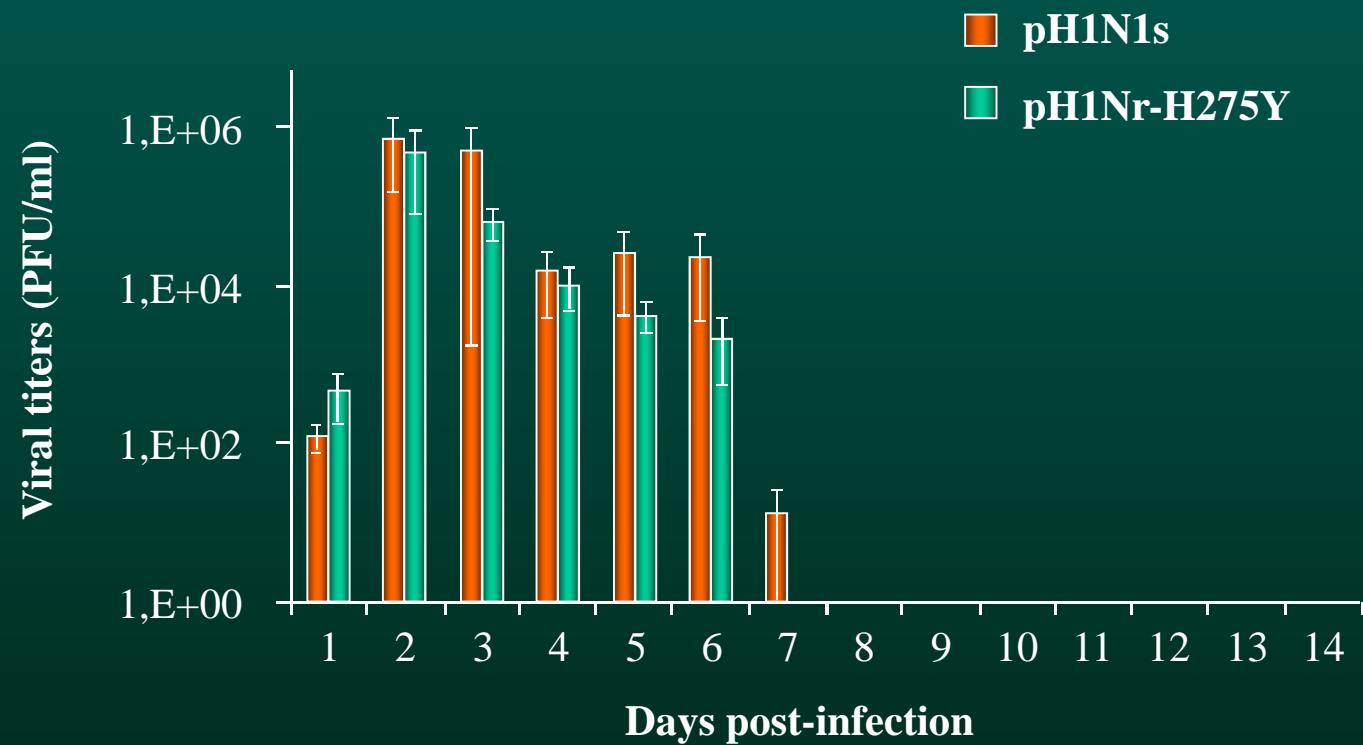
Titres viraux pulmonaires post-infection chez la souris



Température post-infection chez le furet



Titres viraux nasaux post-infection chez le furet



Transmission du mutant H275Y chez le furet

Infected ferrets		Contact ferrets		Aerosol ferrets	
Day 0	Day 14	Day 0	Day 14	Day 0	Day 14
<20	1280	<20	2560	<20	2560
<20	1280	<20	640	<20	<20
<20	640	<20	640	<20	<20
<20	1280	<20	480	<20	<20



Modélisation de la pandémie 2009 au Canada (Risk Analytica)

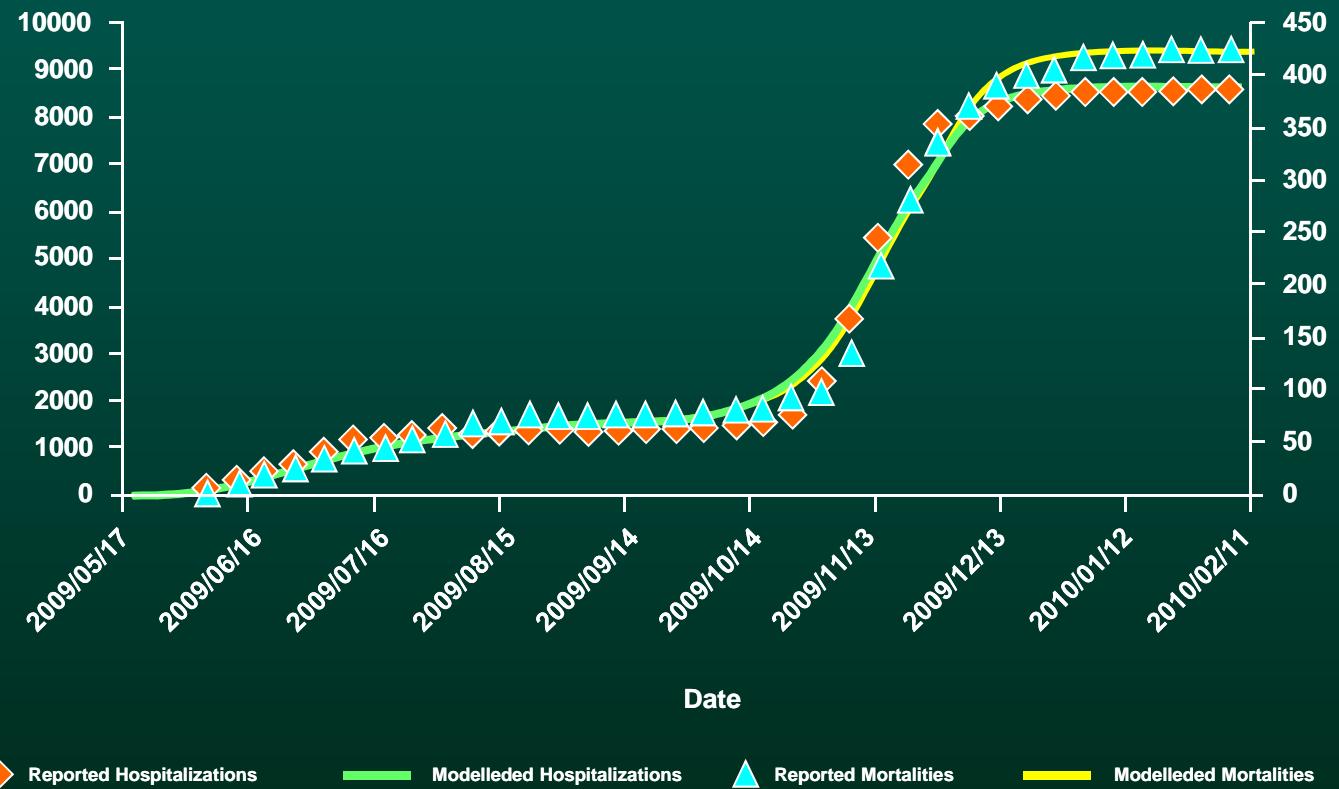
(Age-dependent susceptible-exposed-infected-recovered pandemic model coupled with a macroeconomic model)

A-Facts

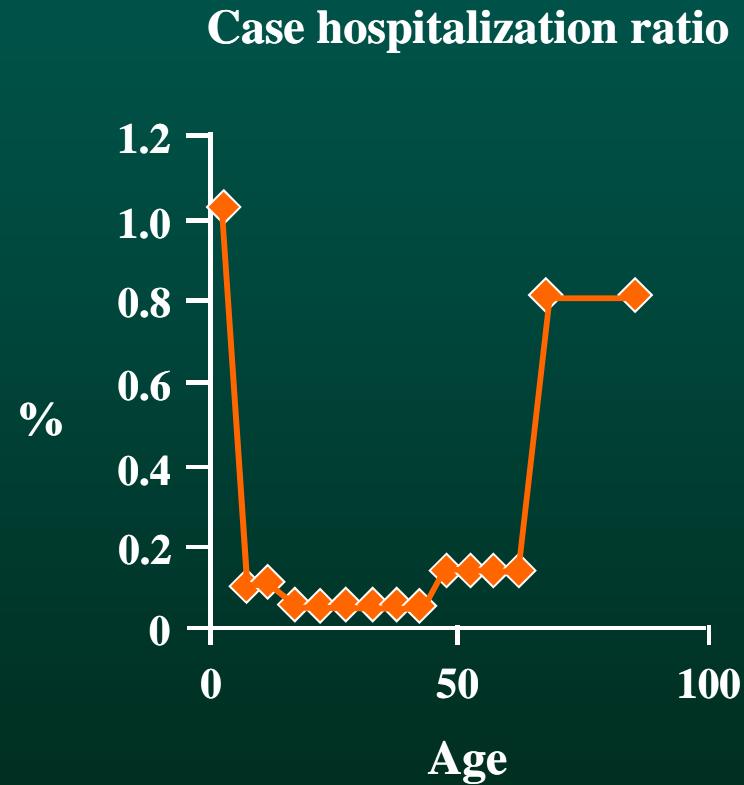
- 8678 hospitalizations, 428 mortalities
- 6.2% were treated, 45% were vaccinated (started late October)
- pH1N1 attack rate of approximately 15%
- 12680 QALYs lost
- Direct health care costs: \$58 million CDN
- Indirect economic impact: \$1.6 billion CDN (0.1% GDP)



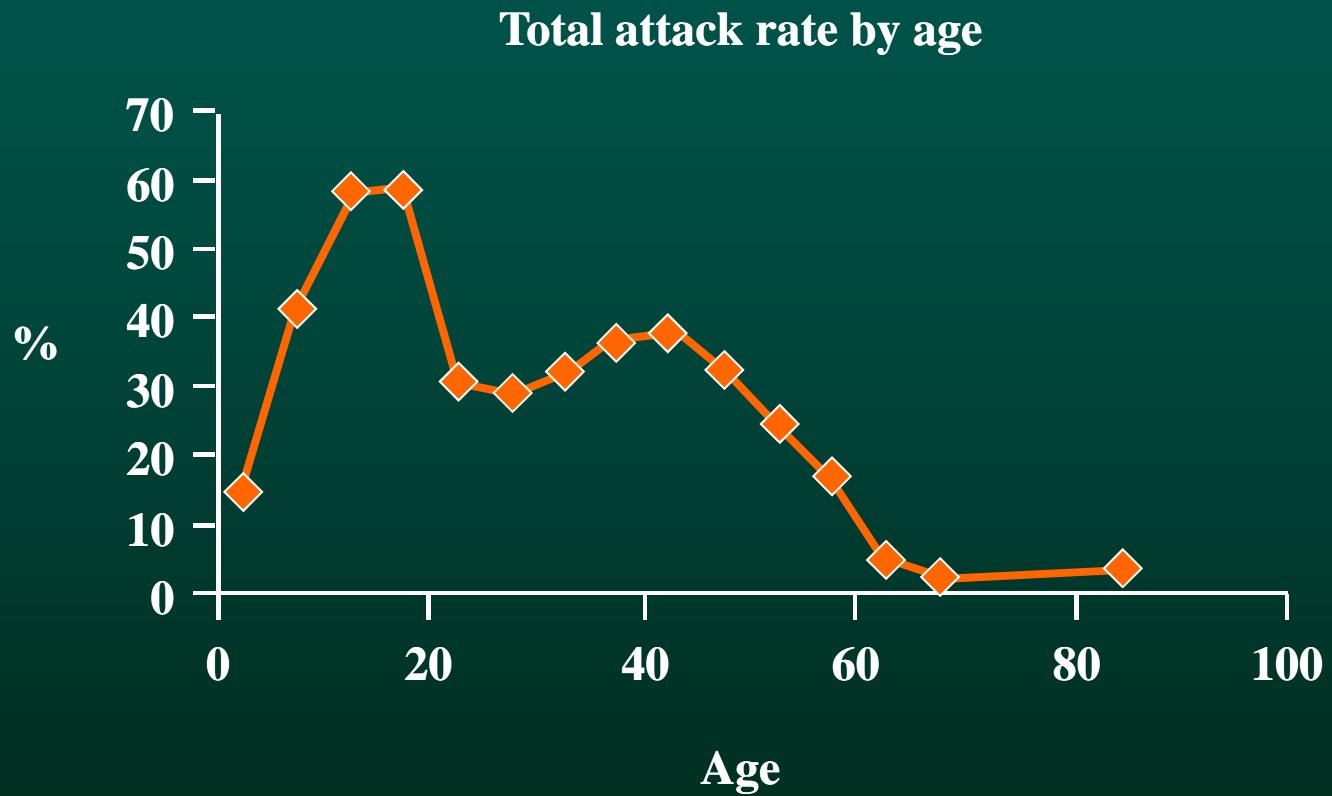
Comparaison de l'hospitalisation (gauche) et de la mortalité (droite) rapportée et modélisée au Canada



Taux d'hospitalisation (gauche) et de mortalité (droite) pour pH1N1 en Ontario



Le taux d'attaque est dépendant de l'âge



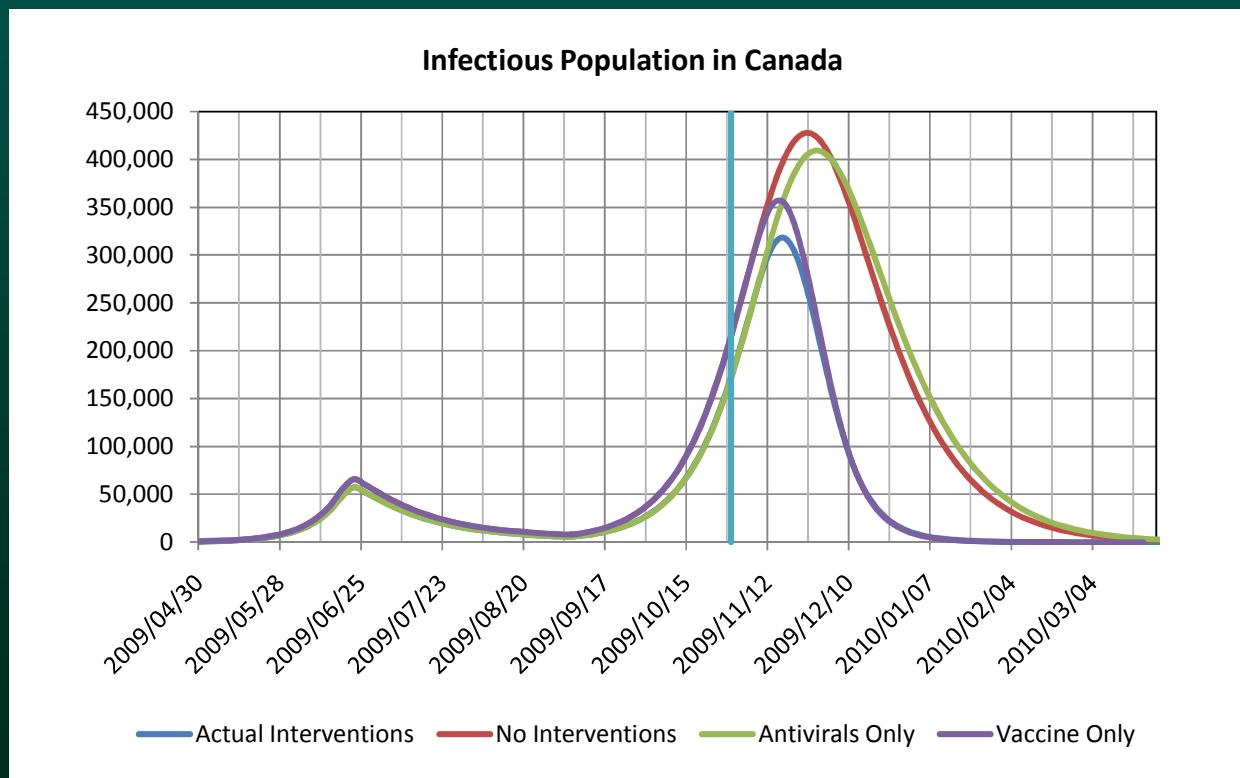
La modélisation de la pandémie 2009 au Canada (Risk Analytica)

B-Interventions

- Hospitalizations decreased by 2x: antivirals (7.6%), vaccine (85.4%), synergy (7%)
- Deaths decreased by 4x: antivirals (55.1%), vaccine (65%), both (20%)
- Antivirals cost-effectiveness (ICER): \$2002 per QALY gained
- Vaccine cost-effectiveness (ICER): \$2076 per QALY gained (\$17317 due to vaccine waste)



La population infectée au Canada selon les interventions actuelles et sans intervention. La ligne verticale indique la disponibilité du vaccin.



La modélisation de la pandémie 2009 au Canada (Risk Analytica)

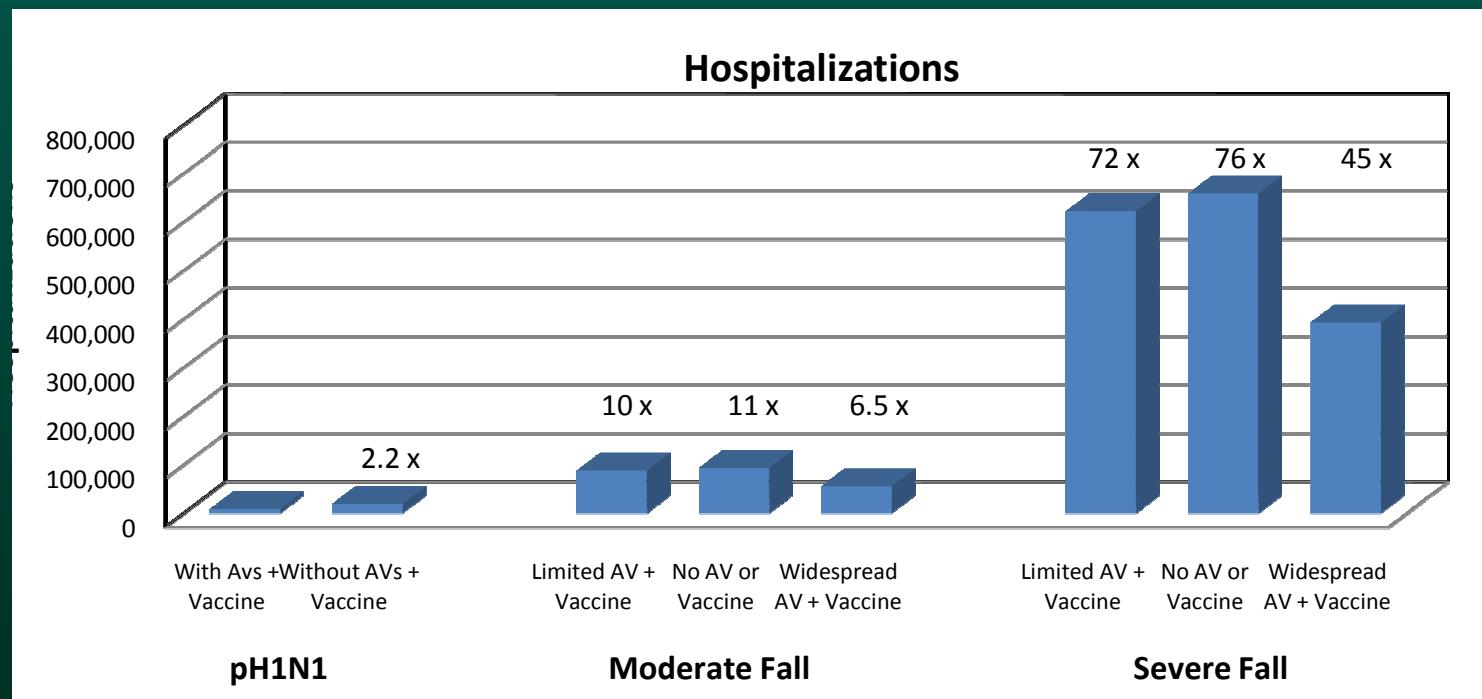
C-Projections*

- Hospitalizations increase by 10x (moderate) and 72x (severe)
- Deaths increase by 32x (moderate) and 209x (severe)
- Vaccine do not contribute much (estimated to arrive 12 weeks after peak)
- Widespread AV use (50% treated, 5% PEP) can significantly decrease hospitalizations and deaths compared to limited AV use (6% treated)

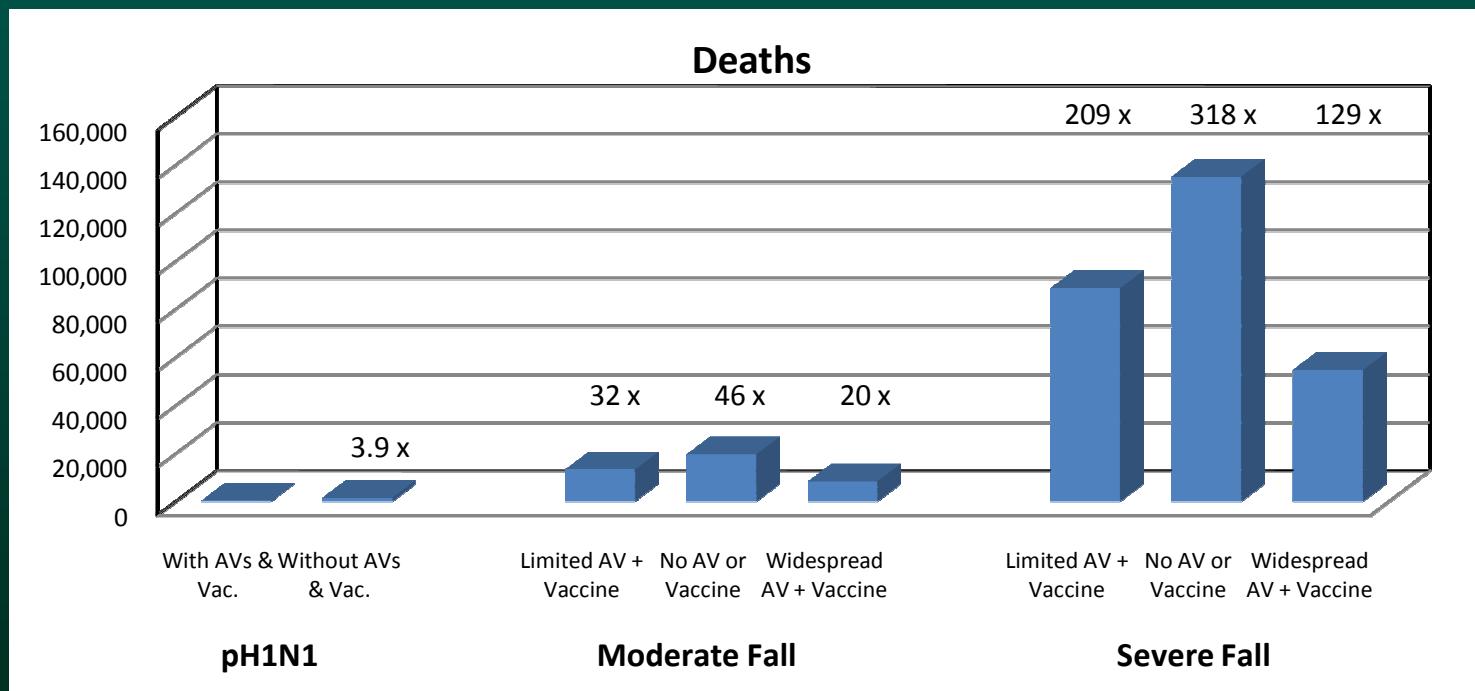
***Fall moderate (1957-58; CFR=0.16%) and severe (1918-19; CFR=1.4%) scenarios with 2009 AV use**



Taux d'hospitalisation lors d'une pandémie automnale modérée et sévère comparé à celui de la pandémie actuelle



Taux de mortalité lors d'une pandémie automnale modérée et sévère comparé à celui de la pandémie actuelle



Conclusions

- Le pH1N1 est un nouveau virus réassortant porcin qui se transmet bien chez l'humain et qui cause une maladie plus sévère chez les femmes enceintes et les sujets avec obésité morbide ou autres conditions sous-jacentes.
- Le mutant pH1N1 H275Y associé à la résistance à l'oseltamivir est virulent dans des modèles animaux mais sa transmission aérienne est réduite.
- Les antiviraux ont un rôle clé qui est synergique à la vaccination en cas de pandémie en réduisant les hospitalisations et surtout les décès.



L'unité de virologie humaine (Québec, Canada)



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