

Effectiveness of Antiviral Stockpiles for Pandemic Preparedness

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Antivirals

- Anti-viral drugs stockpiled by many countries for treatment and prophylaxis
- Treatment effectiveness well documented for various influenza – seasonal & zoonotic H5N1, H7N9
- Prophylaxis evidence from a few controlled studies
- Few field studies from actual deployments
- Policy based on modeling studies

Source Containment

- Containing highly virulent pandemic at earliest sign of localised human-to-human transmission
- Also applicable for targeted containment
 - Essential operations
 - Populations where rapid spread is neither desirable nor manageable
- Two key modelling studies
 - Longini et al, Science, 2005
 - Ferguson et al, Nature, 2005
 - Possibility of success for rapid containment of influenza epicentre if combination strategies used

Differences between Epicenter and Pandemic

	Epicenter	Pandemic
Geography / scale	Point area	Widespread
Aim	Containment	Reduce impact
Command	Direct	Indirect
Resources	Focused	Spread out
Quarantine	Comprehensive	Not routine
Surveillance	Active / detailed	Sampling
Surge capacity	Only in epicenter	Across country
Assistance	Forthcoming	Difficult

Source Containment

- Antiviral prophylaxis for contacts only
 - >90% effective if reproductive number (R_0) <1.25
- Antiviral prophylaxis for contacts and all up to 10km
 - Containing virus with a R_0 of <1.7
- Combined anti-viral prophylaxis and either school and workplace closures or area quarantine
 - R_0 of 1.7-1.8
- Combination of all 3 strategies
 - R_0 of 1.9

Reducing Global Spread

Colizza et al, PLOS Med, 2008

- Redistribution of antiviral drugs
 - Help contain pandemics
 - Reduce the global attack rate
- Non-cooperative strategy can contain a virus with $R_0 < 1.5$
- Redistribution of 25% of stockpiles to countries that do not have stockpiles
 - Pandemic with $R_0 = < 1.9$ may be contained
 - At higher R_0 attack rate reduced by 25%

Onerous Criteria for Containment

- Rapid identification of case
- Rapid and sensitive case detection and prophylaxis
- Effective delivery of prophylaxis
- Sufficient drugs available
- $R_0 < 2$
- Population cooperation
- International collaboration

Ring Prophylaxis Effectiveness Study

- 4 clusters from 22-25 Jun 09
- Total 1175 persons at risk
- Interventions:
 - All suspected cases sent to hospital and isolated
 - Affected groups segregated
 - Post-exposure ring prophylaxis with oseltamivir
 - Continued working (unlike in general population)
- Aim:
 - To determine the effectiveness of post-exposure ring prophylaxis with oseltamivir in reducing flu transmission

Efficacy of Interventions

	Overall
Number of confirmed cases	
Before intervention	75 (6.4%)
After intervention	7 (0.6%)
	(p <0.001)

Reproductive number dropped from
1.91 pre-intervention to
0.11 post-intervention
(p<0.001)

Delaying Onset

McCaw et al, Math Biosci. 2007

- Australian context
- **Treatment based strategy**
 - Does not delay onset of a pandemic appreciably
 - Cannot significantly reduce the attack rate from baseline
- **Combined strategy of contact tracing and targeted post-exposure prophylaxis**
 - Most effective to mitigate impact
 - Delays onset of pandemic by 6-18 months
 - Provide time to develop and distribute a vaccine

Cost-Effectiveness of Antiviral Stockpile

Siddiqui et al, Emerg Infect Dis. UK 2008

- United Kingdom
- Three potential strategies
 - 1) No intervention
 - 2) Treat all patients with AV drugs
 - 3) Test then treat
- Treat-only option** is cost-effective
- Test-treat option** results in moderate gains in QALYs over the treat-only option but at relatively large additional costs
- Conclusion:** Stockpiling sufficient AV drugs to treat all patients would be cost-effective, provided AV drugs are effective at preventing deaths

Prioritized use of Stockpile

Merler et al BMC Infect Dis. Italy 2009

- Antiviral stockpile required for treatment ranges from 10% to 35% of population for R_0 1.4 – 3.
- **Treatment of all cases and prophylaxis of younger individuals:** Significant reduction of the clinical AR
- Stockpiles should treat 25% of populations (assuming R_0 is not >2)
- When antiviral stockpiled exceeds minimum level -> prophylaxis to younger individuals can be incorporated
- When antivirals stockpiled is well below 25% of population -> priority should be based on age-specific case fatality rates.

Combination Strategies

- Problems with individual strategies
 - Not effective enough
 - Socio-cultural-economic impact
 - Resistance
 - Sole source
- Combination strategies provide
 - Synergistic effect
 - Availability of a basket of measures

Impact Mitigation

Halder et al, BMC Public Health. 2010

- Western Australia
- R_0 of 1.5
- Antiviral treatment of 50% symptomatic cases reduced AR from 32.5% to 26%.
- Addition of household prophylaxis reduced AR to **19%**.
- Prophylaxis to close contacts reduced AR to **13%**
- Coupling school closure with the antiviral strategies further reduced epidemic impact

Impact Mitigation

Ferguson et al, Nature, 2006

- Individual strategies
 - School and work place closure
 - Antiviral treatment and prophylaxis
 - Household quarantine
 - Reduce overall AR by 10-35%
 - Reduce peak AR by 20-45%,
- Combination
 - Reduce overall AR by >70%
 - Reduce peak AR by >90%

Impact Mitigation

Duerr et al, BMC Infect Dis. 2007

- **Case isolation and social distancing**
 - Reduce overall AR by 25%
- **Antiviral treatment alone**
 - Reduce AR by 20%
- **Combination of case isolation, social distancing and antiviral treatment**
 - Reduce AR by 40%

Impact Mitigation

Halloran et al, Proc Natl Acad Sci U S A, 2008

Pandemic of R_0 1.9

- **Social distancing alone**
 - Reduce overall AR by 60%
- **Combination**
 - Antiviral treatment and prophylaxis
 - Quarantine
 - Social distancing
 - School closure
 - Reduce overall AR by >90%

Impact Mitigation

Germann et al, Proc Natl Acad Sci U S A. 2006

- **Ro 1.6 pandemic**
 - Individual strategies
 - Prophylaxis
 - Vaccination
 - School closures
 - >80% effective
- **Ro >2.0**
 - Individual strategies
 - 30-60% effective
 - Combination strategies maintained effectiveness at >99%