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Oseltamivir use in an Influenza Outbreak: Linking Pharmacology to Pharmacoeconomics

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BACKGROUND AND OBJECTIVE

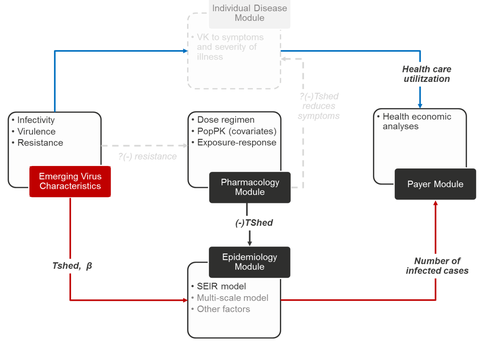
- Simulation models are used widely in pharmacology, epidemiology and health economics. However, there have been no attempts to incorporate models from these disciplines into a single integrated model
- Accordingly, we explored this linkage to evaluate the epidemiological and economic impact of oseltamivir dose optimization in supporting pandemic influenza planning in the US

METHODS

Model

- A health economic (HE) decision analytic model was linked to a previously published pharmacokinetic/pharmacodynamics(PK/PD)-a susceptible-exposed-infected-recovered (SEIR) epidemiologic model [2] which simulated the infected population in an influenza outbreak under different scenarios **(Figure 1)**
- The infected individual produced by SEIR model entered the HE model either as an outpatient or inpatient. Inpatients would be admitted to a general ward or an intensive care unit (ICU), and may experience either pneumonia, sepsis or acute respiratory distress syndrome **(Figure 2)**

Figure 1: Model structure and description



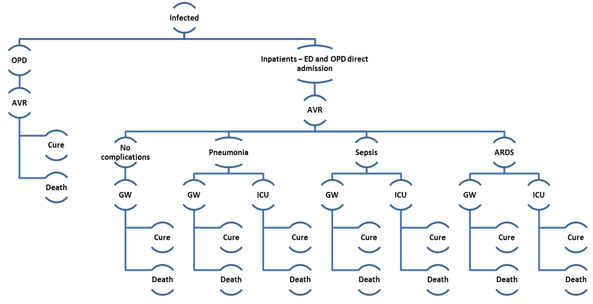
Note: The solid lines indicate that adequate data exists to be able to create semi-mechanistic links to each of adjacent "modules". The dotted lines and light grey describe where significant unknowns remain and are not mature enough to have been incorporated into the current framework.

METHODS

Model inputs & assumptions

- A cost-utility analysis was undertaken based on healthy adults aged 18 to 64 years old in the US from both payer and societal perspectives
- Oseltamivir 75mg or 150mg BID was compared with no treatment at three levels of uptake (25%, 50%, and 80%) for a strain with comparable virulence to typical seasonal-influenza over a 1-year time horizon
- Data inputs for HE model such as branch probabilities, direct medical care cost, direct non-medical care cost, indirect cost (daily productivity loss by age), length of stay were all US-specific while utilities were extrapolated from published literatures
- Assumptions were made as follows:
  - Oseltamivir was prescribed within 48 hours of influenza symptoms
  - All patients were assumed to be 100% adherent to treatment received
  - Patients were assumed to only experience one influenza-related complication.
- Both 1-way and multivariate probabilistic sensitivity analyses (PSA) were conducted to explore model robustness.
- Cost was expressed in 2013 USD.

Figure 2: Health economics model structure

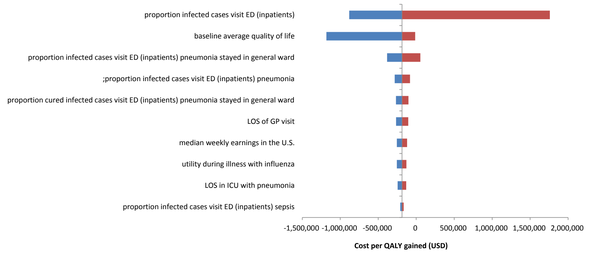


Note: Influenza patients entered the decision analytic model from epidemiology model. They received treatment in outpatient or inpatient setting.

RESULTS

Figure 3. Tornado diagrams (150mg vs. no treatment with 80% uptake of oseltamivir): 1-way sensitivity analysis under two pandemic scenarios

(a) Low virulence and low transmissibility



(b) High virulence and transmissibility

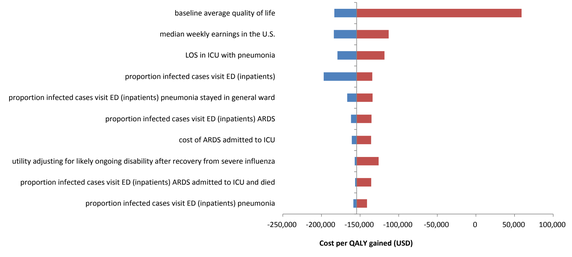


Figure 4. Scatter plots (incremental cost vs. incremental QALY) of 75mg vs. no treatment under societal perspective for (a) Low virulence and low transmissibility and (b) High virulence and high transmissibility

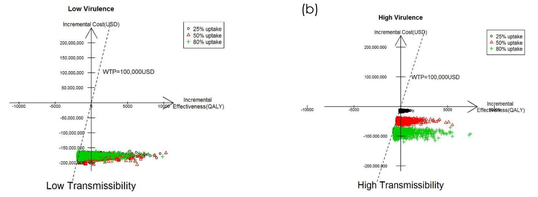


Table 1. Base-case analyses: high-dose vs. no treatment, and standard dose vs. no treatment

Comparators		Δ Costs (payer)	Δ Costs (societal)	Δ Death	Δ LYs	Δ QALYs	Payer perspective: Cost per LY gained	Payer perspective: Cost per QALY gained	Societal perspective: Cost per LY gained	Societal perspective: Cost per QALY gained
Low virulence and low transmissibility										
75 mg vs. no treatment										
	25% uptake	-33,362,767	-89,019,619	-378	366	395	-91,120	-84,559	-243,130	-225,624
	50% uptake	-34,721,953	-97,363,387	-426	413	445	-84,106	-78,106	-235,840	-219,016
	80% uptake	-31,420,000	-95,072,535	-433	420	452	-74,874	-69,542	-226,560	-210,425
150 mg vs. no Treatment										
	25% uptake	-32,200,674	-91,062,835	-400	388	418	-83,062	-77,116	-234,897	-218,083
	50% uptake	-28,748,519	-92,360,189	-433	419	452	-68,534	-63,660	-220,180	-204,521
	80% uptake	-21,237,183	-85,515,601	-438	424	456	-50,086	-46,530	-201,680	-187,361
150 mg vs. 75 mg										
	25% uptake	1,162,092	-2,043,215	-22	22	23	53,971	50,500	-94,893	-88,790
	50% uptake	5,973,434	5,003,199	-7	7	7	899,830	848,005	753,675	710,268
	80% uptake	10,182,817	9,556,934	-5	4	5	2,324,971	2,210,101	2,182,068	2,074,257
High virulence and high transmissibility										
75 mg vs. no treatment										
	25% uptake	-14,167,627	-31,696,343	-193	187	200	-75,836	-71,016	-169,662	-158,879
	50% uptake	-49,309,677	-101,904,191	-617	598	629	-82,495	-78,371	-170,485	-161,963
	80% uptake	-88,899,525	-179,850,525	-1,098	1,063	1,112	-83,610	-79,917	-169,150	-161,678
150 mg vs. no Treatment										
	25% uptake	-24,304,917	-53,631,551	-341	331	349	-73,520	-69,720	-162,230	-153,844
	50% uptake	-63,252,396	-133,577,886	-844	818	856	-77,362	-73,857	-163,374	-155,972
	80% uptake	-95,501,955	-200,976,888	-1,288	1,247	1,302	-76,569	-73,364	-161,133	-154,390
150 mg vs. 75mg										
	25% uptake	-10,137,290	-21,935,208	-148	144	149	-70,510	-67,985	-152,572	-147,108
	50% uptake	-13,942,719	-31,673,695	-227	220	227	-63,408	-61,357	-144,043	-139,384
	80% uptake	-6,602,430	-21,126,363	-190	184	189	-35,881	-34,869	-114,811	-111,573

RESULTS

- Under low virulence and low transmissibility scenarios, compared with no treatment, the use of 75mg and 150mg BID could lead to the reduction in overall direct and indirect costs by saving a substantial amount of life years (LY) and QALYs **(Table 1)**.
- Overall drug costs were offset by the reduction of both direct and indirect costs, making these two interventions cost-saving from both perspectives.
- Both 75 mg BID standard and 150 mg BID high dose oseltamivir therapy were cost-saving from both perspectives **(Table 1)**.
- One-way sensitivity analysis showed that results were sensitive to the proportion of inpatients presented at ED and baseline utility **(Figure 3)**.
- Most results based on 5,000 Monte Carlo simulations were located in the 4th quadrant, implying that the use of oseltamivir was less costly and more effective **(Figure 4)**.

CONCLUSIONS

- High dose oseltamivir has economic value and may have a role in pandemic influenza particularly in high transmissability and requires further investigation.
- Integrating PK/PD-EPI/HE models is achievable. Whilst further refinement of this novelly linked model to better represent the reality is needed, the current study has generated useful insights to support influenza pandemic planning.
- Limitations to be addressed in future iterations include: i) consideration of other interventions such as masks, school closure and influenza vaccine ii) Broadening the model beyond healthy subjects of 18-65 years of age iii) sourcing PK/PD associations with viral shedding duration from patient trials rather than a human inoculation study and iv) using agent based epidemiological modelling methods instead of SEIR models

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