

Point of Care Nucleic Acid Testing for Influenza-Like Illness: A Cost-Consequence Analysis for High-Risk Patients in Primary Care in Germany

Electronic supplementary material

Johannes Pöhlmann^{a,*}, Anika Joecker^b, Tanja Wittki^b, Tray Brown^a, Richard F. Pollock^a,
Jordan Chase^c

^a *Covalence Research Ltd, Harpenden, UK*

^b *Cepheid GmbH, Krefeld, Germany*

^c *Cepheid Inc, Sunnyvale, CA, USA*

*Corresponding author

Name: Johannes Pöhlmann

Postal address: Covalence Research Ltd, Rivers Lodge, West Common, Harpenden,
AL5 2JD, United Kingdom

E-Mail: poehlmann@covalence-research.com

Phone: +44 (0) 20 8638 6525

Tables

Table S1 Downstream resource use and clinical outcomes by treatment status

Outcome	Use/incidence in ... patients, %		Source
	Untreated	Treated	
Influenza A/B			
Hospitalization	1.70	0.70	[1]
ICU Hospitalization	17.90	7.37	[2,3]
MV ICU	52.00	21.41	[2,4]
Pneumonia incidence	1.80	0.70	[1,2]
Mortality	0.13	0.04	[5]
SARS-CoV-2			
Hospitalization	0.97	0.13	[2,6,7]
ICU Hospitalization	36.00	20.41	[2,8]
MV ICU	19.00	10.77	[2,8]
Pneumonia incidence	10.00	5.00	[2]
Mortality	0.97	0.04	[6,7]
RSV			
Hospitalization	0.54	0.54	[2,9]
ICU Hospitalization	13.00	13.00	[10]
MV ICU	10.00	10.00	[2,11]
Pneumonia incidence	10.00	5.00	[2]
Mortality	0.01	0.01	[12]
Any coinfection			
Pneumonia incidence	10.00	5.00	[2]
Mortality	1.00	0.07	[2]
Unknown disease			
Hospitalization	0.39		
ICU Hospitalization	0.08		[2,13]
MV ICU	5.28		
Mortality	0.010		[14]

Abbreviations: ICU, Intensive Care Unit; MV; Mechanical Ventilation; RSV, Respiratory Syncytial Virus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

Note: Probabilities for ICU admission are conditional on having been admitted to hospital first, while probabilities for MV are conditional on prior ICU admission.

Table S2 Results from scenario analyses

Scenario	Outcome	Xpert Xpress	Empiric	Antigen	Send-out PCR
Using consultation and positivity data from week 05/2024 (influenza peak in the 2023/24 season)	Total cost, EUR	82,546,519	92,854,605	94,429,758	140,871,163
	Δ EUR vs. Xpert Xpress	0	10,308,086	11,883,238	58,324,644
	Total cost per tested person, EUR	116	130	133	198
	Δ EUR vs. Xpert Xpress	0	14	17	82
	Total net correct treatment courses, n	553,435	221,195	412,046	150,979
	Δ n vs. Xpert Xpress	0	-332,239	-141,389	-402,455
	Total cost per correct course, EUR	149	420	229	933
	Δ EUR vs. Xpert Xpress	0	271	80	784
	Test cost per correct course, EUR	69	0	67	222
	Δ EUR vs. Xpert Xpress	0	-69	-3	152
Using consultation and positivity data from week 48/2023 (SARS-CoV-2 peak in the 2023/24 season)	Total cost, EUR	58,890,673	60,986,608	71,324,098	58,807,429
	Δ EUR vs. Xpert Xpress	0	2,095,935	12,433,425	-83,244
	Total cost per tested person, EUR	83	86	100	83
	Δ EUR vs. Xpert Xpress	0	3	17	0
	Total net correct treatment courses, n	392,782	236,047	307,776	362,986
	Δ n vs. Xpert Xpress	0	-156,735	-85,006	-29,795
	Total cost per correct course, EUR	150	258	232	162
	Δ EUR vs. Xpert Xpress	0	108	82	12
	Test cost per correct course, EUR	98	0	89	92
	Δ EUR vs. Xpert Xpress	0	-98	-9	-6

Scenario	Outcome	Xpert Xpress	Empiric	Antigen	Send-out PCR
Using consultation and positivity data from week 50/2023 (RSV peak in the 2023/24 season)	Total cost, EUR	67,465,586	71,910,452	80,351,516	82,798,763
	Δ EUR vs. Xpert Xpress	0	4,444,867	12,885,930	15,333,177
	Total cost per tested person, EUR	95	101	113	116
	Δ EUR vs. Xpert Xpress	0	6	18	22
	Total net correct treatment courses, n	493,946	237,098	378,255	360,416
	Δ n vs. Xpert Xpress	0	-256,848	-115,691	-133,530
	Total cost per correct course, EUR	137	303	212	230
	Δ EUR vs. Xpert Xpress	0	167	76	93
	Test cost per correct course, EUR	78	0	72	93
	Δ EUR vs. Xpert Xpress	0	-78	-5	15
Send-out PCR results available within 12h for tests Monday to Thursday	Total cost, EUR	66,259,649	68,225,806	76,337,098	74,799,400
	Δ EUR vs. Xpert Xpress	0	1,966,157	10,077,449	8,539,751
	Total cost per tested person, EUR	93	96	107	105
	Δ EUR vs. Xpert Xpress	0	3	14	12
	Total net correct treatment courses, n	443,600	239,250	347,218	358,561
	Δ n vs. Xpert Xpress	0	-204,351	-96,383	-85,040
	Total cost per correct course, EUR	149	285	220	209
	Δ EUR vs. Xpert Xpress	0	136	70	59
	Test cost per correct course, EUR	87	0	79	93
	Δ EUR vs. Xpert Xpress	0	-87	-8	7

Scenario	Outcome	Xpert Xpress	Empiric	Antigen	Send-out PCR
Send-out PCR results available within 12h for tests Monday to Friday	Total cost, EUR	66,259,649	68,225,806	76,337,098	64,632,715
	Δ EUR vs. Xpert Xpress	0	1,966,157	10,077,449	-1,626,934
	Total cost per tested person, EUR	93	96	107	91
	Δ EUR vs. Xpert Xpress	0	3	14	-2
	Total net correct treatment courses, n	443,600	239,250	347,218	423,267
	Δ n vs. Xpert Xpress	0	-204,351	-96,383	-20,333
	Total cost per correct course, EUR	149	285	220	153
	Δ EUR vs. Xpert Xpress	0	136	70	3
	Test cost per correct course, EUR	87	0	79	79
	Δ EUR vs. Xpert Xpress	0	-87	-8	-8
Send-out PCR results available within 24h for tests Monday to Thursday	Total cost, EUR	66,259,649	68,225,806	76,337,098	84,642,461
	Δ EUR vs. Xpert Xpress	0	1,966,157	10,077,449	18,382,812
	Total cost per tested person, EUR	93	96	107	119
	Δ EUR vs. Xpert Xpress	0	3	14	26
	Total net correct treatment courses, n	443,600	239,250	347,218	295,914
	Δ n vs. Xpert Xpress	0	-204,351	-96,383	-147,686
	Total cost per correct course, EUR	149	285	220	286
	Δ EUR vs. Xpert Xpress	0	136	70	137
	Test cost per correct course, EUR	87	0	79	113
	Δ EUR vs. Xpert Xpress	0	-87	-8	26
Send-out PCR results available within 24h for tests Monday to Friday	Total cost, EUR	66,259,649	68,225,806	76,337,098	74,799,400
	Δ EUR vs. Xpert Xpress	0	1,966,157	10,077,449	8,539,751

Scenario	Outcome	Xpert Xpress	Empiric	Antigen	Send-out PCR
	Total cost per tested person, EUR	93	96	107	105
	Δ EUR vs. Xpert Xpress	0	3	14	12
	Total net correct treatment courses, n	443,600	239,250	347,218	358,561
	Δ n vs. Xpert Xpress	0	-204,351	-96,383	-85,040
	Total cost per correct course, EUR	149	285	220	209
	Δ EUR vs. Xpert Xpress	0	136	70	59
	Test cost per correct course, EUR	87	0	79	93
	Δ EUR vs. Xpert Xpress	0	-87	-8	7
Lower 95% confidence interval bounds for diagnostic accuracy (sensitivity/specificity): - Xpert Xpress - Influenza A/B: 95.5%/97.5% (mean across values for influenza A and B) [15] - SARS-CoV-2: 97%/95% [16] - RSV: 94%/99% [15] - Antigen - Influenza A/B: 64%/96% [17] - SARS-CoV-2: 52% [18]/98.5% [19] - RSV: 77%/95% [17] - Empiric diagnosis - Influenza A/B: 22%/72% [20] (assumed the same for SARS-CoV-2 and RSV) - Send-out PCR - Influenza A/B: 90%/97% [17] - SARS-CoV-2: 93%/98% [21] - RSV: 89%/98% [17]	Total cost, EUR	66,259,649	77,444,729	78,763,167	88,319,987
	Δ EUR vs. Xpert Xpress	0	11,185,079	12,503,518	22,060,337
	Total cost per tested person, EUR	93	109	111	124
	Δ EUR vs. Xpert Xpress	0	16	18	31
	Total net correct treatment courses, n	443,600	194,732	332,435	273,961
	Δ n vs. Xpert Xpress	0	-248,869	-111,166	-169,639
	Total cost per correct course, EUR	149	398	237	322
	Δ EUR vs. Xpert Xpress	0	248	88	173
	Test cost per correct course, EUR	87	0	82	122
	Δ EUR vs. Xpert Xpress				
		0	-87	-4	36

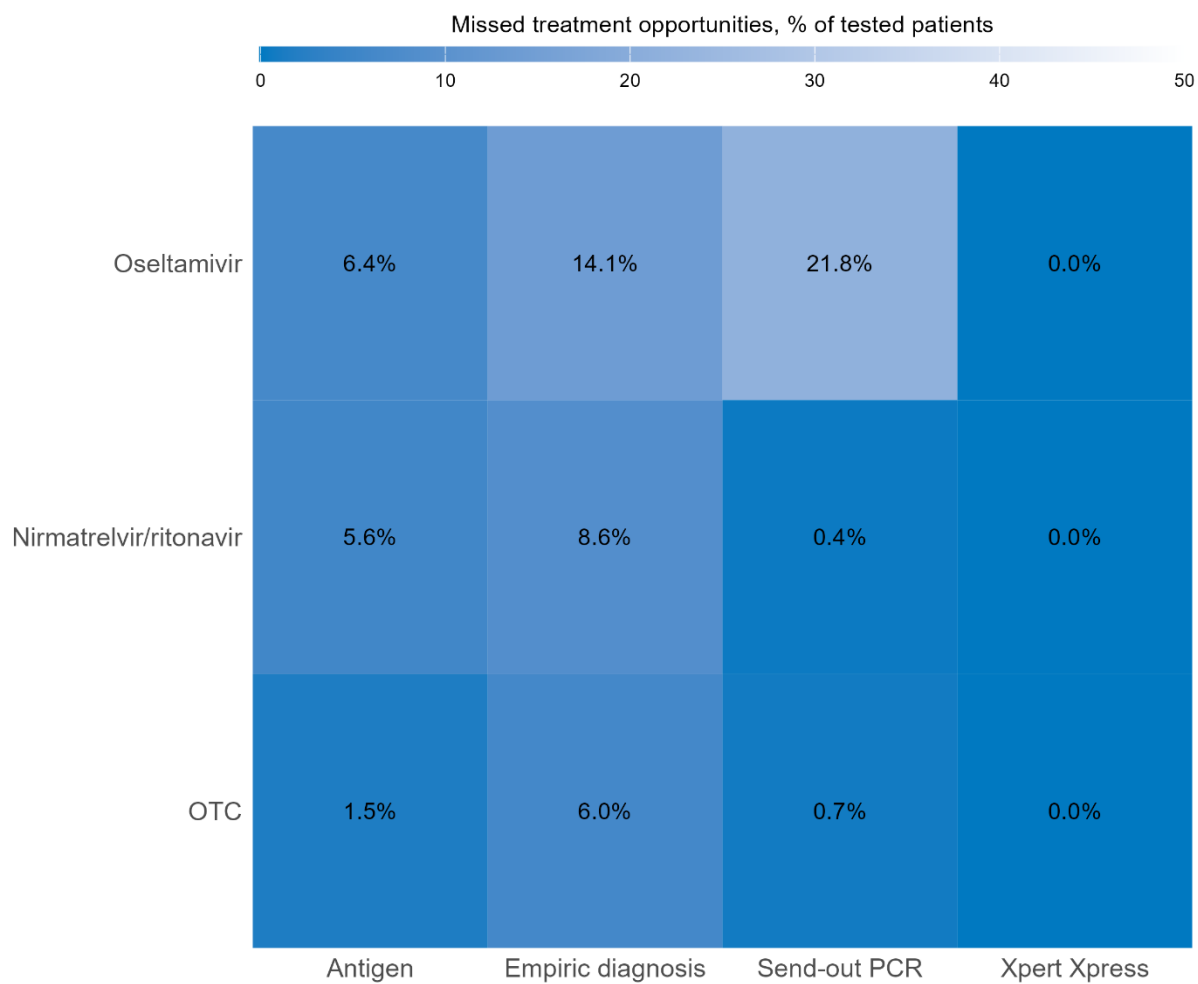
Scenario	Outcome	Xpert Xpress	Empiric	Antigen	Send-out PCR
Upper 95% confidence interval bounds for diagnostic accuracy:	Total cost, EUR	66,259,649	58,279,547	73,918,844	86,082,562
• Xpert Xpress: 100% specificity across all indications [22]	Δ EUR vs. Xpert Xpress	0	-7,980,102	7,659,195	19,822,913
• Antigen:	Total cost per tested person, EUR	93	82	104	121
○ Influenza A/B: 74%/98% [2,17]	Δ EUR vs. Xpert Xpress	0	-11	11	28
○ SARS-CoV-2: 60% [18]/99.2% [19]	Total net correct treatment courses, n	443,600	290,208	360,743	285,439
○ RSV: 87%/98% [17]	Δ n vs. Xpert Xpress	0	-153,393	-82,857	-158,161
• Empiric diagnosis:	Total cost per correct course, EUR	149	201	205	302
○ Influenza A/B: 52%/83% [20] (assumed the same for SARS-CoV-2 and RSV)	Δ EUR vs. Xpert Xpress	0	51	56	152
• Send-out PCR	Test cost per correct course, EUR	87	0	76	117
○ Influenza A/B: 96%/99% [17]	Δ EUR vs. Xpert Xpress	0	-87	-11	31
○ SARS-CoV-2: 100%/100% [21]					
○ RSV: 96%/99% [17]					
48h from symptom onset to presentation for testing	Total cost, EUR	78,645,215	70,768,834	84,700,079	87,302,194
	Δ EUR vs. Xpert Xpress	0	-7,876,381	6,054,864	8,656,979
	Total cost per tested person, EUR	110	99	119	123
	Δ EUR vs. Xpert Xpress	0	-11	9	12
	Total net correct treatment courses, n	365,814	213,263	293,661	279,099
	Δ n vs. Xpert Xpress	0	-152,552	-72,153	-86,716
	Total cost per correct course, EUR	215	332	288	313
	Δ EUR vs. Xpert Xpress	0	117	73	98
	Test cost per correct course, EUR	105	0	93	120
	Δ EUR vs. Xpert Xpress	0	-105	-12	15

Scenario	Outcome	Xpert Xpress	Empiric	Antigen	Send-out PCR
4-day treatment window for oseltamivir	Total cost, EUR	66,259,414	68,225,779	76,336,969	64,119,555
	Δ EUR vs. Xpert Xpress	0	1,966,365	10,077,555	-2,139,859
	Total cost per tested person, EUR	93	96	107	90
	Δ EUR vs. Xpert Xpress	0	3	14	-3
	Total net correct treatment courses, n	443,602	239,250	347,218	426,533
	Δ n vs. Xpert Xpress	0	-204,352	-96,384	-17,069
	Total cost per correct course, EUR	149	285	220	150
	Δ EUR vs. Xpert Xpress	0	136	70	1
	Test cost per correct course, EUR	87	0	79	78
	Δ EUR vs. Xpert Xpress	0	-87	-8	-8
No effect of appropriate treatment on pneumonia and mortality	Total cost, EUR	81,504,701	73,713,752	85,506,899	99,882,157
	Δ EUR vs. Xpert Xpress	0	-7,790,949	4,002,198	18,377,456
	Total cost per tested person, EUR	114	104	120	140
	Δ EUR vs. Xpert Xpress	0	-11	6	26
	Total net correct treatment courses, n	443,600	239,250	347,218	280,527
	Δ n vs. Xpert Xpress	0	-204,351	-96,383	-163,074
	Total cost per correct course, EUR	184	308	246	356
	Δ EUR vs. Xpert Xpress	0	124	63	172
	Test cost per correct course, EUR	87	0	79	119
	Δ EUR vs. Xpert Xpress	0	-87	-8	33

Abbreviations: PCR, Polymerase Chain Reaction; RSV, Respiratory Syncytial Virus; SARS-CoV-2, Severe Acute Respiratory Coronavirus 2.

Figures

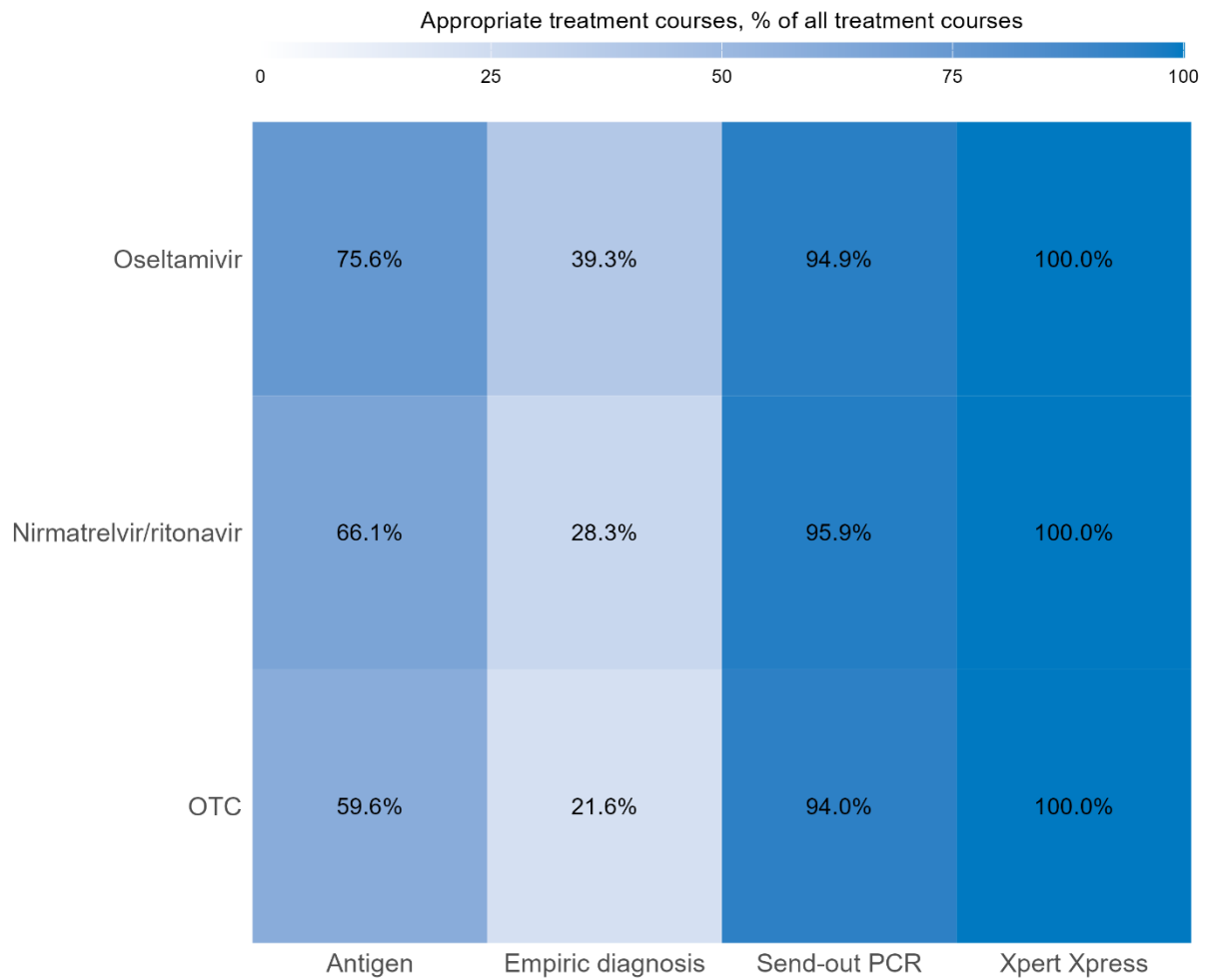
Figure S1 Missed treatment opportunities, by test



Abbreviations: OTC, Over-The-Counter; PCR, Polymerase Chain Reaction.

Note: Darker colors indicate lower values, which for this outcome are better. This is different from the color scale used in Figure S2. Also note that the scale runs from 0% to 50% (not 100%) so differences between tests are easier to see.

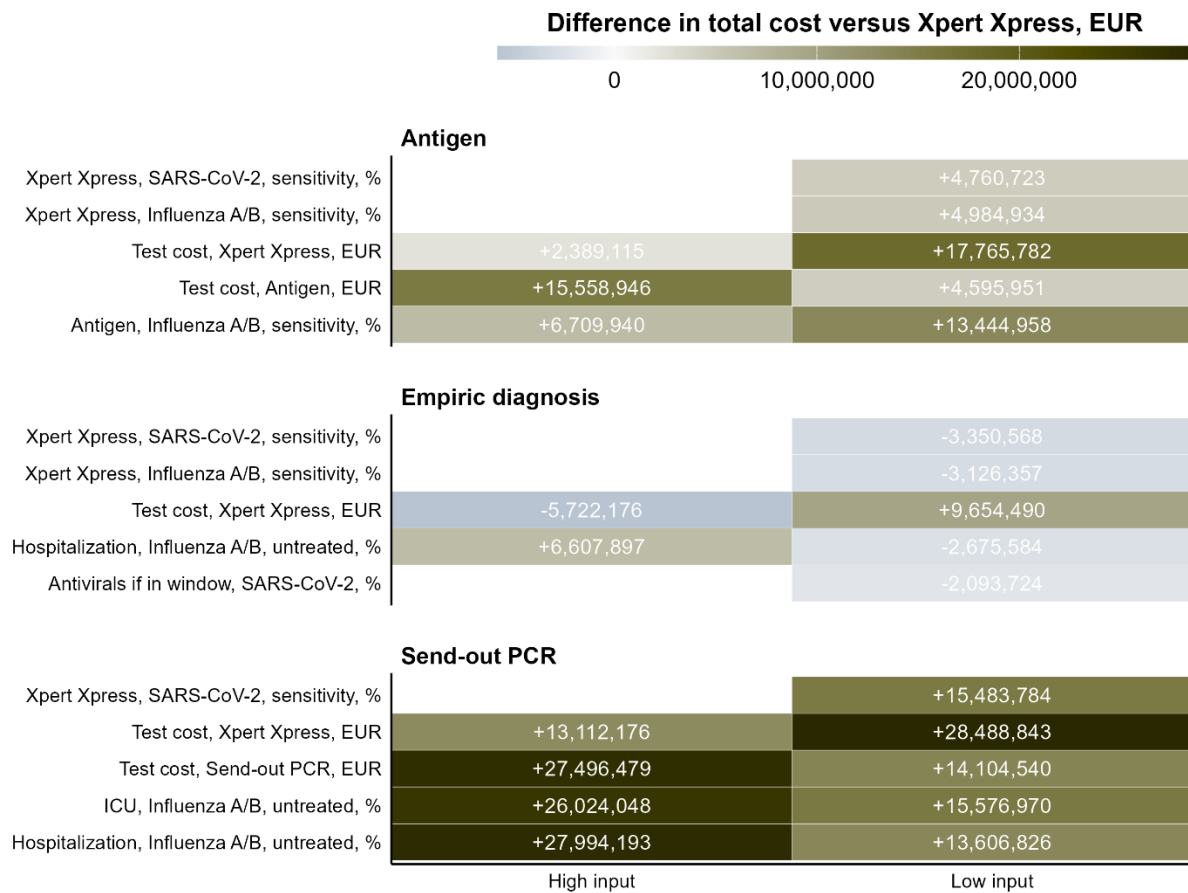
Figure S2 Appropriate treatment courses, by test



Abbreviations: OTC, Over-The-Counter; PCR, Polymerase Chain Reaction.

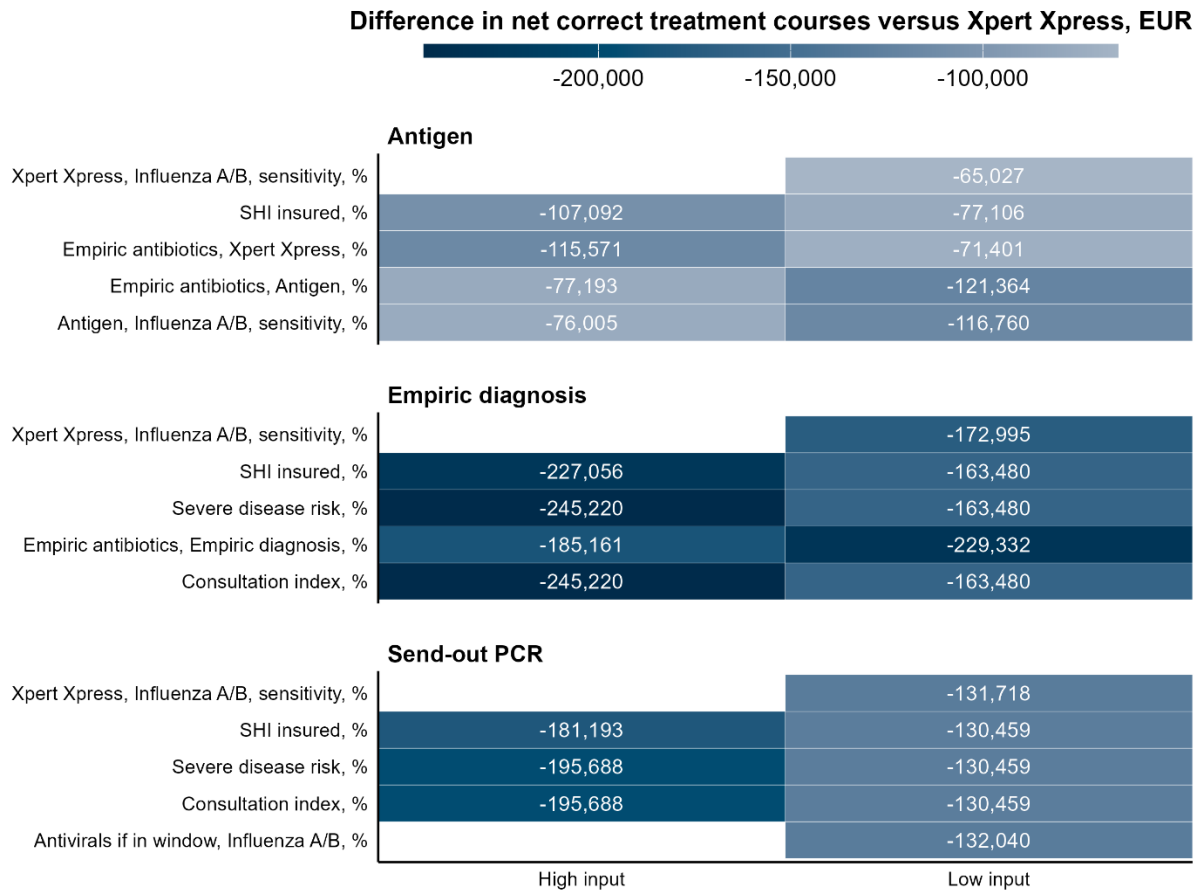
Note: Darker colors indicate higher values, which for this outcome are better. This is different from the color scale used in Figure S1.

Figure S3 Deterministic sensitivity analyses: absolute difference in total costs versus Xpert Xpress



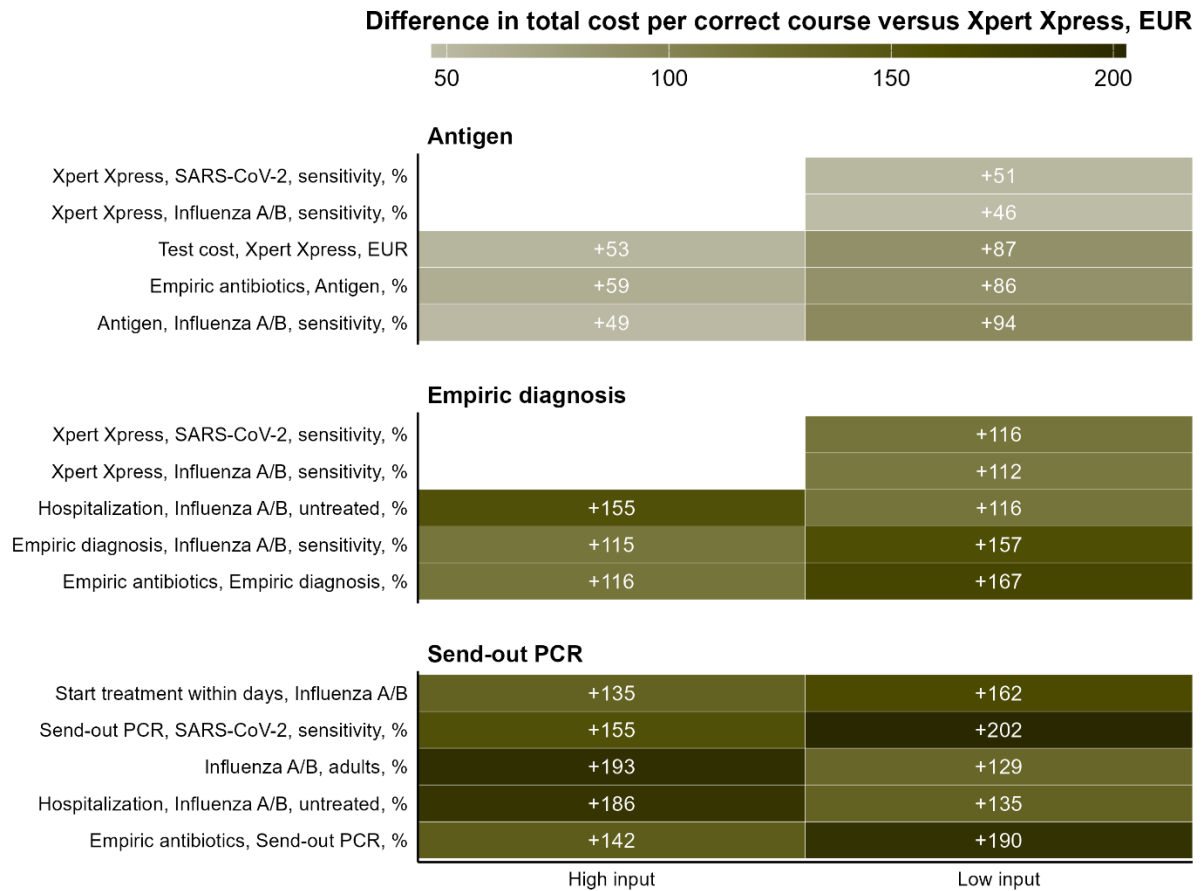
Abbreviations: PCR, Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

Figure S4 Deterministic sensitivity analyses: absolute difference in net correct treatment courses versus Xpert Xpress



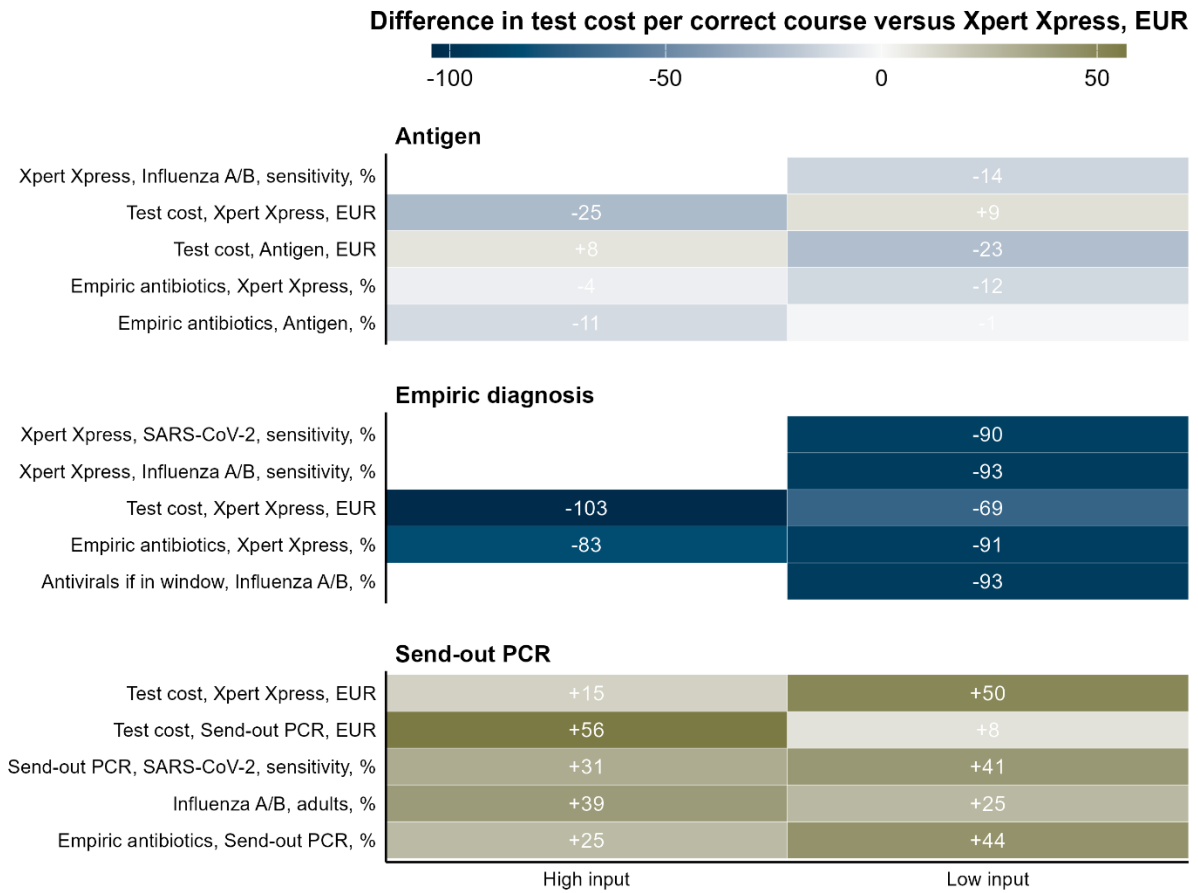
Abbreviations: PCR, Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SHI, Statutory Health Insurance.

Figure S5 Deterministic sensitivity analyses: absolute difference in total cost per correct course versus Xpert Xpress



Abbreviations: PCR, Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

Figure S6 Deterministic sensitivity analyses: absolute difference in test costs per correct course versus Xpert Xpress



Abbreviations: PCR, Polymerase Chain Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

References

1. Kaiser L, Wat C, Mills T, et al (2003) Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 163:1667–1672. <https://doi.org/10.1001/archinte.163.14.1667>
2. Davies S, Boller E, Chase J, et al (2024) A cost-consequence analysis of the Xpert Xpress CoV-2/Flu/RSV plus test strategy for the diagnosis of influenza-like illnesses. *J Med Econ* 27:430–441. <https://doi.org/10.1080/13696998.2024.2313391>
3. Taylor G, Abdesselam K, Pelude L, et al (2016) Epidemiological features of influenza in Canadian adult intensive care unit patients. *Epidemiol Infect* 144:741–750. <https://doi.org/10.1017/S0950268815002113>
4. Rice TW, Robinson L, Uyeki TM, et al (2012) Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. *Crit Care Med* 40:1487–1498. <https://doi.org/10.1097/CCM.0b013e3182416f23>
5. Reacher M, Warne B, Verlander NQ, et al (2023) Oseltamivir is protective for in-patient mortality in PCR confirmed influenza B and influenza A(H3N2) infections in an historic cohort of 1,048 patients hospitalised during the 2016-17 and 2017-18 influenza seasons. *J Infect* 86:256–308. <https://doi.org/10.1016/j.jinf.2023.01.004>
6. Dryden-Peterson S, Kim A, Kim AY, et al (2023) Nirmatrelvir plus ritonavir for early COVID-19 in a large U.S. health system : a population-based cohort study. *Ann Intern Med* 176:77–84. <https://doi.org/10.7326/M22-2141>
7. COVID-NMA initiative (2022) COVID-NMA: summary of results
8. Ohsfeldt RL, Choong CK-C, Mc Collam PL, et al (2021) Inpatient hospital costs for COVID-19 patients in the United States. *Adv Ther* 38:5557–5595. <https://doi.org/10.1007/s12325-021-01887-4>
9. McLaughlin JM, Khan F, Schmitt H-J, et al (2022) Respiratory syncytial virus-associated hospitalization rates among US infants: a systematic review and meta-analysis. *J Infect Dis* 225:1100–1111. <https://doi.org/10.1093/infdis/jiaa752>
10. Ambrosch A, Luber D, Klawonn F, Kabesch M (2023) Focusing on severe infections with the respiratory syncytial virus (RSV) in adults: Risk factors, symptomatology and clinical course compared to influenza A / B and the original SARS-CoV-2 strain. *J Clin Virol* 161:105399. <https://doi.org/10.1016/j.jcv.2023.105399>
11. Choi Y, Hill-Ricciuti A, Branche AR, et al (2022) Cost determinants among adults hospitalized with respiratory syncytial virus in the United States, 2017-2019. *Influenza Other Respir Viruses* 16:151–158. <https://doi.org/10.1111/irv.12912>
12. Hansen CL, Chaves SS, Demont C, Viboud C (2022) Mortality associated with influenza and respiratory syncytial virus in the US, 1999-2018. *JAMA Netw Open* 5:e220527. <https://doi.org/10.1001/jamanetworkopen.2022.0527>

13. Storms AD, Chen J, Jackson LA, et al (2017) Rates and risk factors associated with hospitalization for pneumonia with ICU admission among adults. *BMC Pulm Med* 17:208. <https://doi.org/10.1186/s12890-017-0552-x>
14. Centers for Disease Control and Prevention (2024) Deaths. In: CDC Wonder. <https://wonder.cdc.gov/Deaths-by-Underlying-Cause.html>. Accessed 18 Sep 2024
15. Liu Y-L, Xie T-A, Lin G-L, et al (2022) Diagnostic accuracy of Xpert Xpress Flu/RSV for the detection of influenza and respiratory syncytial viruses. *Jpn J Infect Dis* 75:183–191. <https://doi.org/10.7883/yoken.JJID.2020.987>
16. Lee J, Song J-U (2021) Diagnostic accuracy of the Cepheid Xpert Xpress and the Abbott ID NOW assay for rapid detection of SARS-CoV-2: a systematic review and meta-analysis. *J Med Virol* 93:4523–4531. <https://doi.org/10.1002/jmv.26994>
17. Gentilotti E, De Nardo P, Cremonini E, et al (2022) Diagnostic accuracy of point-of-care tests in acute community-acquired lower respiratory tract infections. A systematic review and meta-analysis. *Clin Microbiol Infect* 28:13–22. <https://doi.org/10.1016/j.cmi.2021.09.025>
18. Smith-Jeffcoat SE, Mellis AM, Grijalva CG, et al (2024) SARS-CoV-2 viral shedding and rapid antigen test performance - respiratory virus transmission network, November 2022–May 2023. *MMWR Morb Mortal Wkly Rep* 73:365–371. <https://doi.org/10.15585/mmwr.mm7316a2>
19. Fragkou PC, Moschopoulos CD, Dimopoulou D, et al (2023) Performance of point-of-care molecular and antigen-based tests for SARS-CoV-2: a living systematic review and meta-analysis. *Clin Microbiol Infect* 29:291–301. <https://doi.org/10.1016/j.cmi.2022.10.028>
20. Dugas AF, Valsamakis A, Atreya MR, et al (2015) Clinical diagnosis of influenza in the emergency department. *Am J Emerg Med* 33:770–775. <https://doi.org/10.1016/j.ajem.2015.03.008>
21. Tsang NNY, So HC, Ng KY, et al (2021) Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. *Lancet Infect Dis* 21:1233–1245. [https://doi.org/10.1016/S1473-3099\(21\)00146-8](https://doi.org/10.1016/S1473-3099(21)00146-8)
22. Cepheid (2023) Xpert® Xpress CoV-2/Flu/RSV plus: instructions for use. <https://www.cephheid.com/content/dam/www-cephheid-com/documents/package-insert-files/xpert-xpress-cov-2-flu-rsv-plus/Xpert%20Xpress%20CoV-2%20FLU%20RSV%20plus%20PI%20302-6991%20Rev.%20B%20EUA.pdf>. Accessed 12 Aug 2024