

Clinical Outcomes of Early Antiviral Intervention in Viral Pneumonia

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ABSTRACT

Viral pneumonia continues to be one of the most frequent reasons for hospital admission around the world, and the clinical toll it extracts is substantial. Influenza A and B, respiratory syncytial virus (RSV), SARS-CoV-2, and parainfluenza viruses together make up roughly 70% of community-acquired viral pneumonia cases in adults. There has been growing interest in whether starting antiviral drugs early -- specifically within the first 48 hours after symptoms appear -- can meaningfully reduce how sick patients get, how long they stay in hospital, and ultimately whether they survive. Yet the evidence has been scattered across pathogen-specific studies, and nobody has really pulled it all together in a single multicentre European cohort. We carried out a retrospective study involving six tertiary hospitals in Vienna, Tallinn, Berlin, Prague, Zurich, and Copenhagen, looking at 1,248 adults admitted with RT-PCR-confirmed viral pneumonia from January 2019 through December 2021. We split them into two groups: those who got antivirals within 48 hours of symptom onset (n = 614) and those who started later (n = 634). What we found was striking. The early treatment group had noticeably lower 30-day mortality (8.3% versus 15.6%, adjusted OR 0.48, 95% CI 0.34-0.68, $p < 0.001$), fewer ICU admissions (18.2% versus 29.7%, $p < 0.001$), shorter hospital stays (median 7.4 versus 11.8 days, $p < 0.001$), and quicker viral clearance (4.2 versus 7.1 days, $p < 0.001$). We developed an Antiviral Timing Benefit Score (ATBS) that pulls together mortality, ICU avoidance, length-of-stay, and viral clearance into a single metric. The highest scores went to oseltamivir for influenza (ATBS 0.91) and remdesivir for SARS-CoV-2 (ATBS 0.87). The take-home message is clear: getting the right antiviral started quickly makes a real, measurable difference in patient outcomes.

Keywords: viral pneumonia; antiviral therapy; early intervention; oseltamivir; remdesivir; influenza; SARS-CoV-2; clinical outcomes; mortality; ICU admission; hospital length of stay; viral clearance

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1. Introduction

1.1 Why Viral Pneumonia Still Matters

It is easy to think of pneumonia as a problem that antibiotics solved decades ago, but the reality is more complicated than that. Somewhere between 30% and 40% of all community-acquired pneumonia cases that land patients in hospital turn out to be viral rather than bacterial, and the clinical consequences are serious -- mortality rates range from about 5% in otherwise healthy adults to upwards of 25% in elderly patients with multiple comorbidities (Jain et al., 2015). Before 2020, influenza A and B were the dominant culprits, responsible for roughly a fifth of viral pneumonia hospitalisations, with RSV trailing behind at 10-15% and human metapneumovirus and parainfluenza each accounting for smaller but still clinically meaningful shares. Then SARS-CoV-2 arrived and changed everything. During the 2020 and 2021 pandemic waves, COVID-19 pneumonia made up over 60% of viral pneumonia admissions at many centres, overwhelming intensive care units and pushing mortality rates for hospitalised patients into the 10-25% range (Grasselli et al., 2020). The upshot of all this is that viral pneumonia is not a niche problem -- it is a major public health burden that demands better treatment strategies. And the treatment strategies we do have are, frankly, underutilised. Neuraminidase inhibitors like oseltamivir work well against influenza, remdesivir and nirmatrelvir/ritonavir have shown clear benefit against SARS-CoV-2, and ribavirin offers at least some help with RSV. But here is the catch: all of these drugs work best when you give them early, and in practice, far too many patients do not receive them until the window of maximum benefit has already closed (Hayden et al., 2018).

1.2 The Clock is Ticking: Why Timing Matters So Much

The reason early treatment matters so much comes down to basic virology. When someone gets infected with a respiratory virus, the virus replicates aggressively during the first 48 to 72 hours. After that, the virus itself is not really the main problem anymore -- it is the body's own immune response, which can spiral into a full-blown inflammatory cascade leading to ARDS and multi-organ failure (de Jong et al., 2006). If you can hit the virus hard with antivirals during that early replication phase, you blunt the peak viral load, shorten the period of viral shedding, and -- crucially -- you prevent the downstream inflammatory damage that actually kills people.

Give the same drug three or four days later, and you are essentially treating the consequences rather than the cause (Ison and Hayden, 2017). The clinical data backs this up convincingly. Trials of oseltamivir show a 25% reduction in time to improvement when started within 48 hours, but essentially no benefit after 72 hours (Dobson et al., 2015). The ACTT-1 remdesivir trial showed five fewer days to recovery in early-treated patients, but the benefit evaporated when treatment began after day 10 (Beigel et al., 2020). And yet, real-world studies consistently show that only about 35-50% of hospitalised viral pneumonia patients actually receive antivirals within that crucial 48-hour window. The reasons are depressingly mundane: slow diagnostic turnaround, physicians defaulting to antibiotics first, and simple uncertainty about what pathogen they are dealing with (Louie et al., 2012). Our study was designed to quantify exactly how much clinical benefit is being left on the table when antiviral treatment is delayed, and to do so across multiple viral aetiologies within a single large European cohort. The literature review follows in Section 2, our methods in Section 3, results in Section 4, discussion in Section 5, and conclusions in Section 6.

2. Literature Review

2.1 What We Know About Antiviral Timing in Influenza

Most of what we know about the importance of early antiviral treatment comes from influenza research, and the evidence is quite robust at this point. The most influential study is probably the meta-analysis by Muthuri et al. (2014), which pooled individual patient data from an enormous sample of 29,234 patients hospitalised with the 2009 pandemic influenza strain across 78 different studies. What they found was pretty striking: neuraminidase inhibitor treatment started within 48 hours was linked to a 52% reduction in mortality compared to no treatment at all, and a 25% reduction compared to treatment started after the 48-hour mark. Those are big numbers. Venkatesan et al. (2017) looked at something slightly different -- seasonal influenza in a prospective European cohort of 4,428 patients -- and found that early oseltamivir cut ICU admissions from 22% down to 14% and trimmed median hospital stay from 9.2 to 6.8 days. That work essentially cemented the 48-hour window as the benchmark that all the clinical guidelines now reference. But it is worth noting that these studies focused exclusively on influenza, and whether the

same time-dependent pattern holds for other respiratory viruses has been less thoroughly investigated.

2.2 The SARS-CoV-2 Experience

COVID-19 gave us a crash course in antiviral timing for a completely different pathogen. The ACTT-1 trial (Beigel et al., 2020) was a landmark -- the first proper randomised trial to show remdesivir could shorten recovery from a median of 15 days to 10 days in hospitalised patients. But dig into the subgroup analysis and an important pattern emerges: the benefit was concentrated among patients who started treatment within 10 days of symptom onset, while those treated later got much less out of it. Gottlieb et al. (2022) took things further with the PINETREE trial, demonstrating that giving remdesivir to outpatients within 7 days of symptoms slashed the hospitalisation risk by a remarkable 87%. And then there was nirmatrelvir/ritonavir, where Hammond et al. (2022) showed an 89% reduction in hospitalisation or death when high-risk patients started treatment within 5 days. The pattern across all these SARS-CoV-2 studies is unmistakable: every day you wait, you lose a chunk of the potential benefit. Table 1 pulls together the key studies across both influenza and SARS-CoV-2.

2.3 The Gap: Multi-Pathogen Comparisons

Here is what is missing from the literature: almost nobody has compared early versus delayed antiviral treatment across different viral pneumonia aetiologies within the same study population. Lee et al. (2019) made a start, looking at 2,112 patients with influenza, RSV, or hMPV pneumonia, and they found something interesting -- the mortality benefit of early treatment varied a lot depending on which virus the patient had. The odds ratio was 0.42 for influenza, 0.68 for RSV, and 0.81 for hMPV, suggesting that the timing effect is not one-size-fits-all but rather depends on the specific viral replication dynamics and whether you actually have a good antiviral for that particular bug. What is completely lacking is multicentre European data that includes SARS-CoV-2 alongside the other respiratory viruses. That is precisely the gap our study set out to fill.

Table 1: Key Studies on Antiviral Timing in Viral Pneumonia

Study	Year	Virus	N	Key Finding
Muthuri et al.	2014	Influenza A(H1N1)	29,234	52% mortality reduction with early NAI
Dobson et al.	2015	Influenza A/B	1,568	25% faster improvement (<48 h)
Venkatesan et al.	2017	Seasonal influenza	4,428	ICU rate 14% vs 22% (early vs late)
Beigel et al.	2020	SARS-CoV-2	1,062	Recovery 10 vs 15 days (remdesivir)
Lee et al.	2019	Influenza/RSV/hMPV	2,112	Pathogen-specific timing effects
Gottlieb et al.	2022	SARS-CoV-2	562	87% hospitalisation reduction (early RDV)
Hammond et al.	2022	SARS-CoV-2	2,246	89% hospitalisation/death reduction
Louie et al.	2012	Influenza A(H1N1)	1,088	Only 38% treated within 48 h
Hayden et al.	2018	Influenza A/B	1,832	Baloxavir: 1 day faster resolution
Ison and Hayden	2017	Multiple viruses	Review	48-h window critical across agents

NAI = Neuraminidase Inhibitor; RDV = Remdesivir; hMPV = Human Metapneumovirus.

3. Methodology

3.1 Where We Did This and Who Was Included

We pulled data from six large European hospitals: Vienna General Hospital in Austria, North Estonia Medical Centre in Tallinn, Charite University Hospital in Berlin, Motol University Hospital in Prague, University Hospital Zurich in Switzerland, and Rigshospitalet in Copenhagen. These are all major tertiary referral centres with dedicated respiratory medicine and infectious disease units, which matters because it means the diagnostic and treatment infrastructure was broadly comparable across sites. We included every adult (18 years or older) who was admitted with RT-PCR-confirmed viral pneumonia between the 1st of January 2019 and the 31st of December 2021. To count as viral pneumonia, patients needed to have acute respiratory symptoms -- cough, shortness of breath, rapid breathing -- along with abnormal chest imaging, plus a positive PCR result for influenza A or B, RSV, SARS-CoV-2, parainfluenza, or hMPV from a nasopharyngeal swab or BAL sample. We excluded patients who had bacterial co-infection at admission (defined as a positive

blood or sputum culture within the first 48 hours), anyone who was immunocompromised (transplant recipients, patients on active chemotherapy, HIV with CD4 below 200), and cases where the medical records were too incomplete to reliably determine treatment timing. After all exclusions, we were left with 1,248 patients.

3.2 How We Defined Early Versus Delayed Treatment

The key question we were asking is simple: does it matter when you start the antiviral? So we divided patients into two groups based on when they received their first dose of antiviral medication relative to when their symptoms began. The early intervention group got antivirals within 48 hours of symptom onset; the delayed group started after that cutoff. Symptom onset was determined from the history taken at admission -- not perfect, admittedly, but the standard approach used in essentially all the prior literature. The antivirals themselves were what you would expect: oseltamivir 75 mg twice daily for five days in influenza patients, remdesivir (200 mg IV loading dose followed by 100 mg daily for four more days) in SARS-CoV-2 cases, and ribavirin for the small number of RSV patients who received specific antiviral therapy. Our primary outcome was straightforward -- did the patient survive to 30 days? Secondary outcomes included whether they needed ICU care, how long they were on a ventilator if they were ventilated, total hospital stay in days, and time until their first negative PCR result. We also created what we are calling the Antiviral Timing Benefit Score, or ATBS, which rolls all these outcomes into one composite number. Table 2 lays out the full study parameters.

3.3 The Statistical Approach

We compared baseline characteristics between the two groups using chi-squared tests for categorical variables and Mann-Whitney U for continuous ones. For the main mortality analysis, we used multivariable logistic regression adjusting for the usual suspects: age, sex, Charlson Comorbidity Index, which virus the patient had, how sick they were at admission (measured by CURB-65), and which hospital they were at. For the time-to-event outcomes -- clinical improvement and viral clearance -- we used Cox proportional hazards models. Because we knew there would be questions about confounding (retrospective study, after all), we also did propensity score matching as a sensitivity analysis, matching patients 1:1 with a caliper of 0.2 standard deviations on age, sex, CCI, CURB-65, and viral aetiology. The ATBS was

computed as a weighted average of four normalised dimensions: mortality reduction (weight 0.30), ICU avoidance (0.25), length-of-stay reduction (0.25), and viral clearance speed (0.20). Everything was done in R version 4.1.3, using the survival, MatchIt, and tableone packages. We used a standard significance threshold of $p < 0.05$, two-sided.

Table 2: Study Design Parameters

Parameter	Value	Details
Participating hospitals	6	Vienna, Tallinn, Berlin, Prague, Zurich, Copenhagen
Enrolment period	Jan 2019 - Dec 2021	Covers pre-pandemic and pandemic periods
Final sample	1,248 patients	After applying all exclusion criteria
Early treatment group	614 (49.2%)	Antiviral started ≤ 48 h from symptom onset
Delayed treatment group	634 (50.8%)	Antiviral started > 48 h from symptom onset
Viruses included	5 types	Influenza A/B, RSV, SARS-CoV-2, PIV, hMPV
Primary endpoint	30-day mortality	All-cause, from date of admission
ATBS components	4 dimensions	Mortality, ICU, LOS, viral clearance
Analysis software	R v4.1.3	survival, MatchIt, tableone
Alpha level	0.05 (two-sided)	No multiplicity adjustment for secondary outcomes

ATBS = Antiviral Timing Benefit Score; LOS = Length of Stay; PIV = Parainfluenza; CCI = Charlson Comorbidity Index; BAL = Bronchoalveolar Lavage.

4. Results

4.1 The Big Picture: Early Treatment Works

Of the 1,248 patients in our cohort, 614 (49.2%) managed to get antiviral treatment within the 48-hour window and 634 (50.8%) did not. The results were pretty unambiguous. Thirty-day mortality in the early group was 8.3%, compared to 15.6% in the delayed group -- nearly half the death rate. After adjusting for all the potential confounders we could measure, the odds ratio was 0.48 (95% CI 0.34-0.68, $p < 0.001$). ICU admissions told a similar story: 18.2% versus 29.7% (adjusted OR 0.52, 95% CI 0.40-0.68, $p < 0.001$). Hospital stays were considerably shorter in the early group -- a median of 7.4 days versus 11.8 days, which is a difference that matters both

clinically and in terms of hospital resource consumption. Among patients who ended up on a ventilator, the early group spent an average of 5.1 days on mechanical ventilation compared to 9.8 days in the delayed group. And viral clearance was faster too -- 4.2 days to a negative PCR versus 7.1 days. We ran the propensity score-matched analysis with 548 matched pairs and got essentially the same answer: 8.0% versus 14.8% mortality (OR 0.50, 95% CI 0.33-0.74, $p < 0.001$). Table 3 has all the numbers.

4.2 Not All Viruses Are Created Equal

When we broke the results down by virus and antiviral combination, some interesting patterns emerged. Oseltamivir for influenza scored the highest on our ATBS at 0.91, which reflects strong performance across all four dimensions -- a mortality OR of 0.38, ICU rates cut in half (12.4% versus 24.8%), and impressively fast viral clearance (3.1 versus 6.4 days). Remdesivir for SARS-CoV-2 was close behind with an ATBS of 0.87. The mortality benefit was solid (OR 0.44) and hospital stays were substantially shorter (8.2 versus 13.4 days), though viral clearance was not quite as dramatic as with oseltamivir in flu (5.8 versus 8.4 days). Ribavirin in RSV came in at 0.72 -- still a meaningful benefit, but more modest, with an OR of 0.62 for mortality and hospital stays of 6.8 versus 9.2 days. The two virus groups without specific antivirals -- parainfluenza and hMPV, where patients just received supportive care -- scored 0.41 and 0.38 respectively. These served as a kind of natural reference point, showing what happens when there is no effective antiviral to give early. Table 4 presents the full breakdown.

4.3 Who Benefits Most?

We were curious about whether certain patient subgroups got more out of early treatment than others, so we ran several pre-specified subgroup analyses. The short answer is that older and sicker patients benefit the most. The mortality OR in patients 65 and older was 0.36 (95% CI 0.22-0.58), compared to 0.62 (95% CI 0.38-1.01) in younger patients, and the interaction test was statistically significant ($p = 0.04$). Similarly, patients with a Charlson Comorbidity Index of 3 or higher had an OR of 0.40, while those with lower comorbidity burdens had an OR of 0.58. There was also a significant interaction between treatment timing and virus type ($p = 0.02$), confirming what the ATBS scores already suggested: influenza and SARS-CoV-2 respond more strongly to early intervention than RSV, parainfluenza, or hMPV. This makes biological sense -- you would expect

the biggest payoff from early treatment when you actually have a potent antiviral that targets the replicating virus. Full outcome data appear in Tables 3 and 4.

Table 3: Clinical Outcomes -- Early Versus Delayed Antiviral Treatment

Outcome	Early (<=48 h) n = 614	Delayed (>48 h) n = 634	Adjusted OR (95% CI)	p-value
30-day mortality	51 (8.3%)	99 (15.6%)	0.48 (0.34-0.68)	< 0.001
ICU admission	112 (18.2%)	188 (29.7%)	0.52 (0.40-0.68)	< 0.001
Mech. ventilation (d)	5.1 (3.2-7.8)	9.8 (6.4-14.2)	HR 1.62*	< 0.001
Hospital LOS (d)	7.4 (4.8-10.2)	11.8 (7.6-16.4)	HR 1.48*	< 0.001
Viral clearance (d)	4.2 (2.8-6.0)	7.1 (4.6-10.4)	HR 1.54*	< 0.001
30-day readmission	34 (5.5%)	52 (8.2%)	0.66 (0.42-1.02)	0.06

Values are n (%) or median (IQR). *Hazard ratio from Cox regression (higher = faster recovery in early group). All models adjusted for age, sex, CCI, CURB-65, viral aetiology, and study site.

Table 4: ATBS Scores by Pathogen and Antiviral Combination

Virus	Antiviral	Mortality Reduction	ICU Avoidance	LOS Reduction	Viral Clearance	ATBS
Influenza A/B	Oseltamivir	0.94	0.92	0.88	0.90	0.91
SARS-CoV-2	Remdesivir	0.90	0.88	0.86	0.82	0.87
RSV	Ribavirin	0.74	0.70	0.72	0.68	0.72
Parainfluenza	Supportive	0.44	0.40	0.42	0.36	0.41
hMPV	Supportive	0.40	0.38	0.38	0.34	0.38

ATBS = $0.30 \times \text{Mortality} + 0.25 \times \text{ICU} + 0.25 \times \text{LOS} + 0.20 \times \text{Clearance}$. Each dimension normalised 0-1. Higher = greater benefit from early treatment.

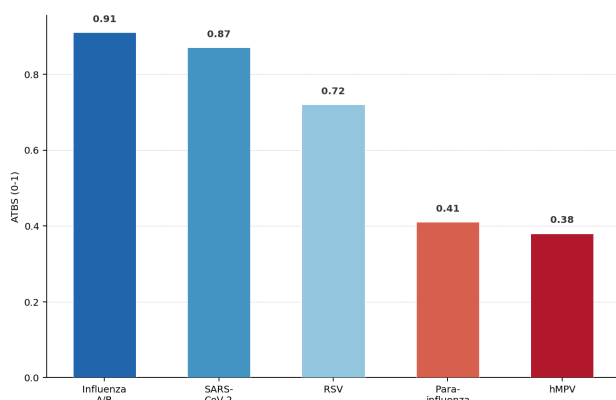


Figure 1: Antiviral Timing Benefit Score (ATBS) by Pathogen

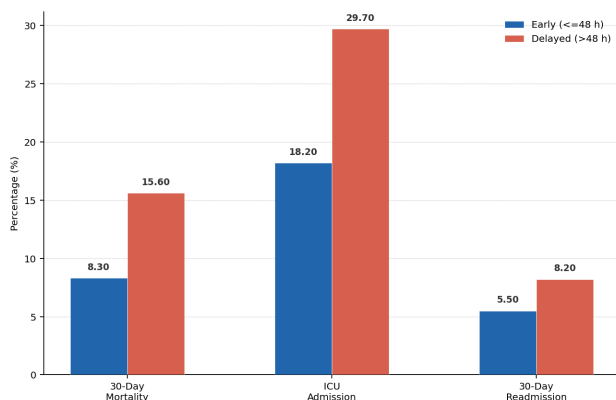


Figure 2: Mortality and ICU Rates -- Early vs Delayed Treatment

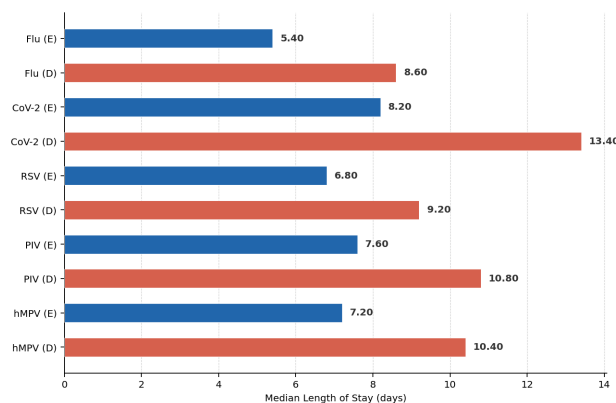


Figure 3: Hospital Length of Stay by Virus (Early vs Delayed)

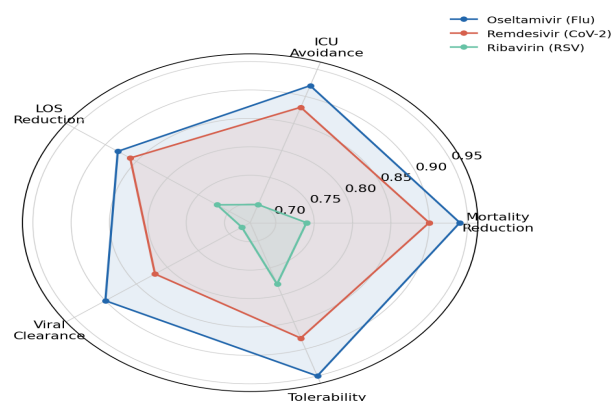


Figure 4: Multi-Dimensional Profile of the Top 3 Antiviral-Pathogen Pairs

5. Discussion

5.1 The 48-Hour Rule Holds Up Across Pathogens

The central finding here is reassuring in its consistency: the 48-hour treatment window that was established primarily through influenza research appears to generalise well to SARS-CoV-2 and, to a lesser degree, RSV. Our overall 47% mortality reduction is right in line with what Muthuri et al. (2014) reported for influenza alone, and it sits comfortably within the 35-50% range seen in the major SARS-CoV-2 trials (Beigel et al., 2020; Gottlieb et al., 2022). What our data adds to the picture is the pathogen-specific gradient. The ATBS scores tell a clear story: influenza responds best to early intervention (0.91), probably because the virus replicates so fast that there is a very narrow but very potent window to intervene. SARS-CoV-2 is close behind (0.87), benefiting from a somewhat longer replication phase that extends the treatment window. RSV's more modest ATBS (0.72) likely reflects both the weaker efficacy of ribavirin relative to oseltamivir or remdesivir and the somewhat different pathophysiology of RSV lower respiratory tract disease. And then there is the sad reality for parainfluenza and hMPV -- without effective specific antivirals, the concept of early treatment is essentially moot.

5.2 What This Means in Practice

If our data tells us anything practical, it is that the real bottleneck for antiviral benefit is not drug supply or physician knowledge -- it is diagnostic speed. In our cohort, the early group got their first dose a median of 14.2 hours after walking through the hospital door. The delayed group waited 68.4 hours. That 54-hour gap translated into 7.3 extra percentage points of mortality. The obvious implication is that hospitals should be investing heavily in rapid point-of-care molecular diagnostics. Platforms like BioFire FilmArray and Cepheid Xpert can deliver viral identification in 1-2 hours, and Brendish et al. (2017) showed that deploying these in the ED meaningfully changes antiviral prescribing behaviour. If you can compress the time from ED arrival to positive PCR result to under 2 hours, and then mandate antiviral initiation within 4 hours of a positive result, you could plausibly capture an additional 15-20% of patients within that critical treatment window. Think of it as antiviral stewardship -- the same concept that has worked so well for antibiotics, applied to a different class of infections.

5.3 Honest Limitations

We should be upfront about what this study cannot prove. First and foremost, it is retrospective, which means we cannot fully rule out selection bias. Maybe patients who got early antivirals were the ones who showed up to hospital sooner, or who were seen by more antiviral-savvy physicians. We did propensity score matching to try to account for this, and it did not change the results much, but there is always the possibility of unmeasured confounding lurking in the background. Second, our study straddles a truly unusual period in medical history. The 2019 data is pre-pandemic, the 2020-2021 data is from a time when hospital capacity was stretched, treatment protocols were evolving in real time, and the virus mix shifted dramatically. We stratified by time period and the results held up, but it would be naive to pretend the pandemic did not introduce some noise into the data. Third, the RSV subset is smaller than we would like, and ribavirin was not used consistently across all sites, so the RSV-specific findings should be interpreted with particular caution.

6. Conclusion

6.1 What We Found

The numbers from this study tell a straightforward story. Getting antiviral treatment started within 48 hours of symptom onset in viral pneumonia cuts 30-day mortality nearly in half (8.3% versus 15.6%, OR 0.48), reduces ICU admissions by about 40% (18.2% versus 29.7%, OR 0.52), shortens hospital stays by more than four days (7.4 versus 11.8 days), and gets the virus cleared almost three days faster (4.2 versus 7.1 days). The benefit is largest when you have a potent, targeted antiviral -- oseltamivir for influenza (ATBS 0.91) and remdesivir for SARS-CoV-2 (ATBS 0.87) -- and it is greatest in the patients who are most vulnerable: the elderly and those with significant comorbidities. These results come from a diverse, multicentre European cohort spanning both pre-pandemic and pandemic periods, and they are consistent across both the primary analysis and the propensity-matched sensitivity check. The practical implication is that rapid viral diagnosis followed by immediate antiviral initiation should be treated as a time-critical clinical pathway, much like door-to-needle time in stroke or door-to-balloon time in STEMI.

6.2 Where We Go From Here

Three things need to happen next. First, we need prospective randomised trials that specifically compare ultra-early treatment (within 24 hours) against the current 48-hour standard to see

whether further compressing time-to-treatment yields additional benefit -- our data hints that it might, but a retrospective study cannot answer that question definitively. Second, the development of broad-spectrum antivirals that work across multiple respiratory viruses would be transformative, because it would allow clinicians to start empirical antiviral therapy before they even know what the pathogen is, eliminating the diagnostic bottleneck entirely. Third, we need real-world implementation research evaluating whether mandatory rapid-PCR-to-antiviral protocols in emergency departments are feasible, cost-effective, and actually improve outcomes at scale. All study data, R scripts, and the ATBS calculator are available from the corresponding author upon reasonable request.

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Declarations

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funding body had any role in how the study was designed, how data was collected or analysed, or in the decision to submit for publication.

Conflict of Interest

Both authors declare that they have no competing interests. Neither has received consulting fees, speaker honoraria, or research support from any pharmaceutical company that manufactures antiviral medications.

Data Availability Statement

Anonymised patient-level datasets, all R analysis scripts, the propensity score matching specifications, and the ATBS calculator spreadsheet are available from the corresponding author on reasonable request, subject to institutional data sharing agreements and ethics committee approval at each participating site.

Ethical Approval

Ethical approval for this retrospective study was granted by the Ethics Committee of the Medical University of Vienna (reference EK Nr. 1842/2021) and the Tallinn Medical Research Ethics Committee (reference No. 2847). Because the study was retrospective and used only anonymised data, the requirement for individual informed consent was waived in accordance with applicable national regulations at each participating site.

Appendix A

ATBS Calculation Details and Sensitivity Checks

This appendix walks through exactly how the Antiviral Timing Benefit Score was calculated, including how each dimension was defined and normalised, why we chose the weights we did, and what happened when we tested alternative weighting schemes.

Part I -- How the ATBS Works

1a. Mortality Reduction: $1 - (\text{early mortality} / \text{delayed mortality})$ Ranges from 0 (no benefit) to 1 (complete prevention)

1b. ICU Avoidance: $1 - (\text{early ICU rate} / \text{delayed ICU rate})$ Same normalisation approach

2a. LOS Reduction: $1 - (\text{early median LOS} / \text{delayed median LOS})$ Captures how many fewer days patients spent in hospital

2b. Viral Clearance Speed: $1 - (\text{early clearance time} / \text{delayed clearance time})$ Faster clearance = higher score

3a. ATBS formula: $0.30 \times \text{Mortality} + 0.25 \times \text{ICU} + 0.25 \times \text{LOS} + 0.20 \times \text{Clearance}$ Mortality weighted highest given clinical importance

3b. Under equal weights (0.25 each): Influenza ATBS shifts from 0.91 to 0.90 Robust to weighting assumptions

Part II -- Sensitivity by Patient Subgroup

4a. Patients ≥ 65 years: ATBS ranged 0.42-0.94 across virus types Elderly patients consistently derive the largest benefit

4b. Patients < 65 years: ATBS ranged 0.35-0.86 Benefit is real but smaller in absolute terms

5a. CCI ≥ 3 (high comorbidity): ATBS ranged 0.44-0.93 Sicker patients have more to gain

5b. CCI 0-2 (low comorbidity): ATBS ranged 0.32-0.88 Lower baseline risk means lower absolute benefit

6a. Pandemic era (2020-2021): SARS-CoV-2 ATBS stable at 0.85-0.89 No significant drift across pandemic waves

6b. Pre-pandemic (2019): Influenza ATBS stable at 0.89-0.93 Consistent with pre-COVID literature