Original Article

Cost-Effectiveness of Stock Epinephrine Autoinjectors on Commercial Aircraft

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What is already known about this topic? Epinephrine is mandated in all US aircraft emergency medical kits, and is provided in ampule (but not autoinjector) form. There are strong lobbying efforts by the food allergy advocacy community to stock autoinjectors on commercial aircraft.

What does this article add to our knowledge? A model providing epinephrine autoinjector twin-packs in addition to the ampule in the medical kit is decidedly cost-effective, with a high value-based cost ceiling and a per-passenger annual cost of $0.08.

How does this study impact current management guidelines? Though the necessity of adding supplemental epinephrine in the form of an autoinjector to commercial aircraft requires further study, the policy could be cost-effective.

BACKGROUND: In-flight food-allergic reactions are rare events, but given increasing reports, grass-root advocates have lobbied to replace aircraft emergency kit epinephrine ampules with autoinjectors.
OBJECTIVE: To evaluate the cost-effectiveness of stock epinephrine on commercial aircraft.
METHODS: We conducted a Markov model with microsimulation of food-allergic individuals over an 80-year time horizon to evaluate the cost-effectiveness of supplementing airline medical kits with epinephrine autoinjectors (eg, providing autoinjector twin-packs in addition to the epinephrine ampule in the medical kit), versus not doing so, using a per-plane annual value-based cost ceiling of $338 (the value-based ceiling for school stock epinephrine). We assumed that autoinjector availability reduced fatality risk by 10%.
RESULTS: Equipping all commercial aircraft with autoinjectors cost $2,470,422/year ($0.08/passenger-at-risk), from a societal perspective and when distributed over all at-risk travelers. Over the model horizon, the supplemental autoinjector strategy cost $32,329.29 (standard deviation [SD], $4024.32) versus $32,326.70 (SD $4024.29), produced 26.8917 quality-adjusted life-years (QALYs) (SD, 2.9720) versus 26.8915 (SD, 2.9725), with a lower fatality rate (0.00012; SD, 0.01095 vs 0.00015; SD, 0.1225) versus the ampule-only strategy. The incremental cost-effectiveness ratio of supplemental airline epinephrine autoinjectors was $10,766/QALY in the base-case analysis. The supplemental model remained cost-effective at a willingness to pay threshold of $100,000/QALY if it produced a minimum 1.4% annual food allergy fatality risk reduction, and dominated if it lowered diversion risk or event-related medical care costs-per-event by 10%, respectively.
CONCLUSIONS: Under base-case scenarios, an airline supplemental stock epinephrine model is cost-effective, with a high value-based cost-ceiling and low annual cost per passenger-at-risk of $0.08. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2270-6)

Key words: *Autoinjector; Anaphylaxis; Cost-effectiveness; Simulation; In-flight medical emergency; Quality of life; Health state utility; Food allergy fatality; Anaphylaxis; Allergic reaction; Value-based price*

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Abbreviations used
FAA- Federal Aviation Administration
ICER- Incremental cost-effectiveness ratio
IME- In-flight medical emergency
QALY- Quality-adjusted life-year
SD- Standard deviation
WTP- Willingness to pay

In-flight medical emergencies (IMEs) are a relatively common event. The incidence of IME is approximately 1 per 604 flights (24-130 IMEs per 1 million passengers).[1] Respiratory and cardiovascular events account for 17% of IMEs, though 2% of all IMEs result from reported allergic reactions. IMEs resulting in diversions occur in approximately 4.4% (95% CI, 4.3% to 4.6%) of events, at a highly variable cost between $20,000 and $725,000 depending on the circumstance.[1]

Food allergies affect between 4% and 9% of children and may persist into adulthood.[2-4] Although novel strategies to treat peanut allergy by desensitizing individuals show promise,[5,6] at present there is no cure for food allergy and patients remain at risk for anaphylaxis from accidental exposure. Thus, there is a prominent role for the carriage and potential use of self-injectable epinephrine as a primary treatment of symptoms from an accidental exposure, and there has been a surge in legislation supporting anaphylaxis awareness that has improved access to a "stock" source of epinephrine available in places such as schools and certain public entities (eg, food service and other public establishments). There are recent emerging data regarding the health economics of epinephrine and anaphylaxis management. Although the role of reflex emergency medical services (EMS) activation has been questioned in the setting of appropriately treated and resolved allergic reactions, early epinephrine is a bedrock of anaphylaxis management.[7] Device price and accessibility are major present issues, given both expensive devices and device shortages in a current marketplace that is dysfunctional.[8] A recent analysis calculated that a $24 value-based cost for a twin-pack of self-injectable epinephrine is cost-effective,[9] and when epinephrine is considered a shared resource in the school setting, annual acquisition epinephrine costs of $338 or lower are also cost-effective.[10]

For several years, there has been a push from the advocacy community to lobby the government and airline industry to mandate that US airlines carry epinephrine autoinjectors, given concerns that reported in-flight allergic emergencies do occur, and that having an autoinjector device would be of benefit to help facilitate potential treatment of allergic passengers.[11] Per the Air Carrier Act of 1986, the Federal Aviation Administration (FAA) requires that emergency medical kits must include 1 mL of 1:1000 epinephrine for injection, which is typically provided as a needle/syringe and ampule of epinephrine.[1] The cost-effectiveness of epinephrine autoinjectors in this scenario has not been previously evaluated. Therefore, we performed this analysis to evaluate annual epinephrine autoinjector device acquisition cost per commercial aircraft that would be cost-effective as an emergency epinephrine source for use in passengers having an in-flight food-allergic reaction.

METHODS

Markov-model (n = 100,000 per strategy) Monte Carlo microsimulations of individuals with food allergies over an 80-year time horizon were performed using TreeAge Pro 2018 to evaluate the cost-effectiveness of supplemental airline epinephrine autoinjectors (eg, providing each commercial aircraft autoinjector twin-packs in addition to the ampule form of epinephrine already in the standard medical kit) (Figure 1). Markov modeling is frequently used in economic simulations of health care strategies because it allows evaluation of iterative risks experienced by cohorts of individuals with unique health care needs over both short- and longer-term time horizons. Total epinephrine autoinjector acquisition costs per aircraft (n = 7309 registered commercial aircraft in the United States)[12] in the base case were modeled after a recently described value-based cost ceiling for acquisition costs for shared stock epinephrine devices in the school system (a model where devices were shared across at-risk lives, but on a smaller scale vs air travel), with a ceiling of $338 per plane.[10] As air travelers (771 million)[13] comprise the same age ranges as the general population, the model began during infancy with costs and quality-adjusted life-years (QALYs)[14] equally discounted at 3% per annum and incorporation of age-adjusted mortality.[15,16] Although some passengers take multiple flights per year, our model considered the risk as independent for each individual flight segment that a passenger may have flown (given we modeled a device acquisition requirement for each commercial aircraft), and thus risk was evaluated at the level of total enplanements, which implies that a passenger could be counted multiple times across all segments he or she flew. All costs were expressed in 2018 US dollars (as of January 1, 2018).[15] Rates of food allergy fatality were modeled with the base-case assumption that supplemental epinephrine autoinjectors produced a 10% risk reduction in fatality rates of airline passengers with food allergy.[17] Models included additional costs of personal self-injectable epinephrine treatment[18] and treatment of allergic reactions[19] with or without supplemental airline epinephrine, from a societal perspective (Table I). For the supplemental airline epinephrine autoinjector strategy market availability of epinephrine autoinjectors was assumed. Subjects experiencing spontaneous or therapy-induced tolerance were not included as travelers with food allergy. Travelers experienced a 7% annual rate of accidental food allergen exposure (inclusive of in-flight and nonflight exposures) with a 1% annual rate of severe allergic reactions (inclusive of reactions both during flight and unrelated to travel).[20] Risks and costs of airline diversion[1] were included in sensitivity analyses to identify minimum risk reduction associated with cost-effective practice. This study involved simulation of subjects and circumstances and as such was exempt from institutional review board approval.

RESULTS

Base case

The base model, assuming a 4% prevalence of food allergy, resulted in 30,840,000 travelers with food allergy each year potentially at risk for in-flight anaphylaxis. Presuming a ceiling for supplemental epinephrine autoinjector acquisition cost of $338 per aircraft, this resulted in a total annual cost of $2,470,422. When these costs were distributed among at-risk food-allergic individuals, from a societal perspective, the cost of the supplemental airline autoinjector was $0.08 per at-risk subject per year.

The supplemental airline epinephrine autoinjector strategy cost $32,329.29 (standard deviation [SD], $4024.32) versus $32,326.70 (SD, $4024.29) over the model horizon, and produced 26.8917 QALYs (SD, 2.9720) versus 26.8915 (SD,

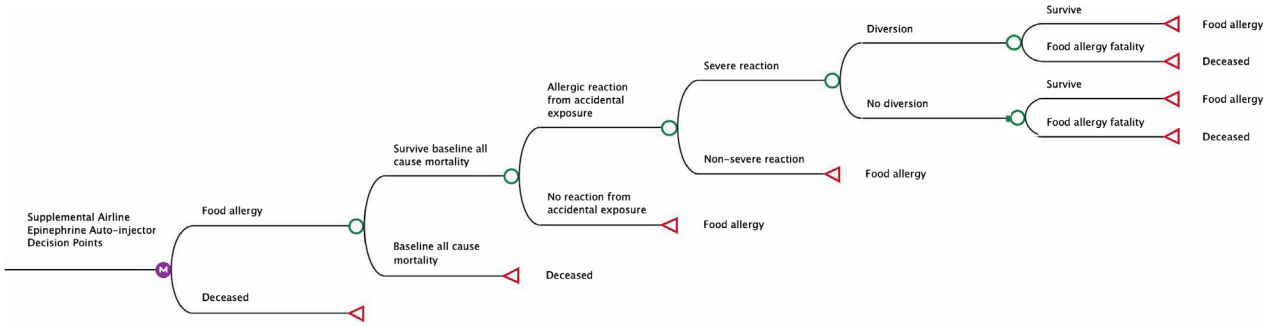


FIGURE 1. Supplemental airline epinephrine autoinjector decision points. Subjects with food allergy traveling in aircraft with undesignated epinephrine autoinjectors experience a 10% risk reduction in food allergy fatality rate in the base case. Patients experiencing severe reactions incurred costs associated with emergency department visits and risks of subsequent hospitalization for anaphylaxis.

TABLE I. Simulation model variables and inputs

Variable	Model reference (sensitivity range)	Source
US Life Table	National Vital Statistics Reports, April 2017	Arias et al[16]
Food allergy fatality	5-19 y: 3.25 per million person years (95% CI, 1.73-6.10; sensitivity 3.25-33) 20 y and older: 1.81 per million person years (95% CI, 0.94-3.45; sensitivity 1.81-18.1)	Umasunthar et al[17]
Rate of accidental food exposure and symptoms in persons with food allergy	7% per year (sensitivity; 5% to 45%)	Neuman-Sunshine et al[20]
Airline passengers (annual)	771 million	Bureau of Transportation Statistics[13]
Commercial aircraft fleet	7309	Aeroweb Forecast International's Aerospace Portal[12]
Rate of aircraft diversion for in-flight medical emergencies	4.4% (95% CI, 4.3% to 4.6%)	Martin-Gill et al[1]
Cost of aircraft diversion	$20,000 (sensitivity $20,000-$725,000)	Martin-Gill et al[1]
Rate of emergency department visit for severe symptoms in persons with food allergy	1% per year (sensitivity; 0.5% to 3.5%)	Neuman-Sunshine et al[20]
Hospitalization after emergency department visit for anaphylaxis	35% (sensitivity; 5% to 45%)	Robinson et al[21]
Personal epinephrine autoinjector cost	$715 (95% CI, $685-$743)	Shaker et al[18] US Department of Labor, Bureau of Labor Statistics[15]
Annual cost of epinephrine acquisition per aircraft	$338	Shaker and Greenhawt[10]
Hospitalization cost	$5899 (95% CI, $5732-$6066)	Patel et al[19] US Department of Labor, Bureau of Labor Statistics[15]
Emergency department visit cost	$691 (95% CI, $689-$693)	Patel et al[19] US Department of Labor, Bureau of Labor Statistics[15]
Start age	0 y (sensitivity 0-8 y)	
Cycle length	1 y	
Annual discount rate	0.03 (sensitivity 0-0.03)	
Negative health state influence for food allergy	−0.09 (sensitivity−0.02 to −0.11)	Carroll and Downs[14]

CI, Confidence interval.

TABLE II. Cost-effectiveness of supplemental airline epinephrine autoinjectors

	Cost	Effectiveness (QALY)	Net monetary benefit ($)	Food allergy fatality	Incremental Cost per passenger at risk (model horizon)	Incremental Effectiveness	ICER
No supplemental airline autoinjector							
Mean	$32,326.70	26.8915	$2,656,820.98	0.00015			
Std Dev	$4024.29	2.9725	$294,169.71	0.01225			
Supplemental airline autoinjector					$2.58	0.0002	$10,766
Mean	$32,329.29	26.8917	$2,656,842.38	0.00012			
Std Dev	$4024.32	2.9720	$294,117.56	0.01095			

Monte Carlo microsimulations were performed (n = 100,000 per strategy compared) to evaluate incremental cost-effectiveness of a supplemental autoinjector strategy ($Cost_A - Cost_B / Effectiveness_A - Effectiveness_B$).
ICER, Incremental cost-effectiveness ratio; *QALY*, quality-adjusted life-year.

2.9725) when compared with a strategy without supplemental epinephrine (Table II). Fatalities, albeit already very low at baseline, were lower in the supplemental model than in the model without supplemental epinephrine (0.00012; SD, 0.01095 vs 0.00015; SD, 0.1225). The incremental cost-effectiveness ratio (ICER) of supplemental airline epinephrine autoinjectors was $10,766/QALY in the base-case analysis.

Sensitivity analyses

In sensitivity analyses, if supplemental epinephrine autoinjectors produced a minimum 1.4% risk reduction in the annual food allergy fatality risk of passengers with food allergy, then the strategy remained cost-effective at a willingness to pay (WTP) threshold of $100,000/QALY (Figure 2). In the base-case analysis with widely distributed epinephrine autoinjector acquisition costs across all at-risk passengers, the value-based price ceiling (WTP = $100,000/QALY) could reach $2469 per aircraft each year. The ICER fell to $6406 for supplemental airline autoinjectors if the population at risk for anaphylaxis was modeled at 10% of the traveling public. If it was assumed that an additional $100,000 was budgeted annually for device training and educations materials, the ICER of the supplemental autoinjector model was $15,088 (ICER of $25,513 if $2,000,000 budgeted annually for training and education materials).

If a 10% risk reduction was also modeled for airline diversions ($20,000 per diversion) attributable to an allergic in-flight event, the supplemental airline epinephrine autoinjector model dominated the analysis in all probabilistic sensitivity iterations across distributions of fatality risk and autoinjector costs. Excluding diversions, a 10% cost reduction of subsequent emergency care or hospitalizations also led to a dominated analysis with supplemental airline epinephrine autoinjectors as the optimal strategy. If the model assumed only 200 million airline travelers each year, the ICER of the supplemental autoinjector strategy was $53,241/QALY. If this low air travel utilization rate was combined with a low rate of food allergy risk modeled at 2%, the ICER of supplemental airline epinephrine was $105,498/QALY. Assuming a more conservative estimate that 52%[22] of the US population (328,228,996 persons)[23] has flown at least once in the past year, the ICER of supplemental autoinjectors was $62,218/QALY. Exclusion of subsequent costs of emergency care, hospitalization, and acquiring personal epinephrine from each strategy did not increase the ICER of supplemental airline epinephrine autoinjector above $20,000/QALY. Additional sensitivity analyses (shown in Figure 3) demonstrated that supplemental epinephrine was cost-effective across multiple assumptions provided epinephrine autoinjector acquisition costs were less than $2469 per aircraft each year.

DISCUSSION

In-flight allergic reactions are a rare occurrence but do occur, and may be under-reported in large series tracking documented events, compared with allergy-specific survey studies of self-reported in-flight events.[24] There have been a paucity of studies on in-flight food-allergic emergencies, all of which have a common theme of reported epinephrine underutilization for potentially severe events, as well as lack of flight crew assistance with such events.[24,25] Although the FAA mandates an epinephrine source on every commercial aircraft emergency medical kit, this is most frequently supplied as an ampule to be extracted with a syringe.[1] However, such extraction requires preparation before injection, which may create significant opportunities for medical error and delay in epinephrine administration.[26-28] Access to supplemental airline epinephrine autoinjectors on all flights has been proposed as a way to potentially improve epinephrine delivery by nonmedical as well as medical providers.[11,26] Routine supply of autoinjectors on commercial airlines may provide significant benefit during allergic emergencies in flight, as physician assistance is only provided in 48% of IMEs, a factor that could impact the ability to effectively draw up epinephrine from an ampule.[29] Furthermore, because emergency medical kits on US flights must include both epinephrine 1:1000 and 1:10,000 solutions, this may further pose confusion as to the correct ampule to choose, and delay the appropriate administration the drug when indicated.[1] To date, no US airline has routinely stocked an epinephrine autoinjector across their flights, though kits from the market leader in supplying airline emergency medical kits have had this option available.[30] Although passengers with allergy risks may carry a personal autoinjector, supplemental autoinjectors in flight are an attractive strategy because many individuals with known anaphylaxis risk do not carry self-injectable epinephrine at all times. Without the availability of supplemental epinephrine autoinjectors, a lack of education and training in use of epinephrine ampules and appropriate management of in-flight allergic emergencies could potentially increase the risk that passengers experiencing anaphylaxis would not receive appropriate or timely treatment.

Given this constraint, our analysis is unique as we propose a supplemental model to circumvent this pitfall, meaning that additional epinephrine autoinjectors would be acquired and

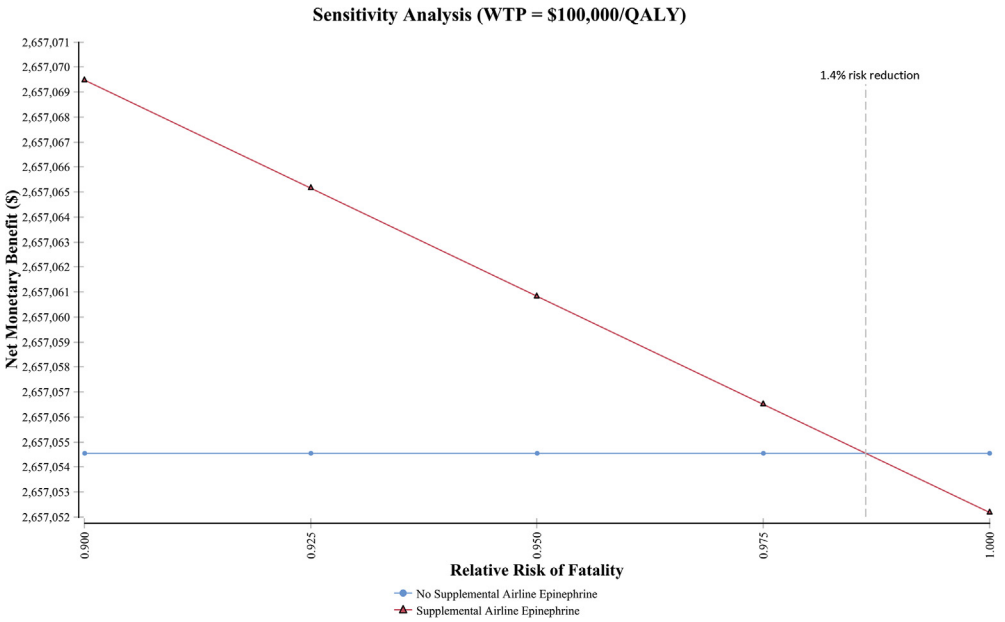


FIGURE 2. Sensitivity analysis of fatality relative risk. At a marginal fatality risk reduction of 1.4%, the devices are cost-effective at total epinephrine autoinjector acquisition costs of $338 per aircraft. The red line indicates the supplemental epinephrine autoinjector strategy and the blue indicates a strategy without supplemental epinephrine autoinjectors. If the fatality risk reduction associated with supplemental epinephrine is greater than 1.4%, then the supplemental epinephrine strategy is associated with greater net-monetary benefit and is a preferred strategy. Note that net monetary benefit (NMB) is a measure synthesizing both cost and quality-adjusted life-years (QALYs). For NMB, QALYs are converted to dollars at a rate of $100,000/QALY. *WTP*, Willingness to pay.

maintained in addition to the ampule in standard medical kit aboard most US commercial aircraft. The present analysis demonstrates cost-effectiveness with annual per-plane epinephrine autoinjector acquisitions costs in excess of that recently modeled in school systems using a similar shared-resource model of epinephrine access. This model clearly demonstrates that a strategy of supplemental stock airline epinephrine can be cost-effective with an ICER below $20,000/QALY, which is well

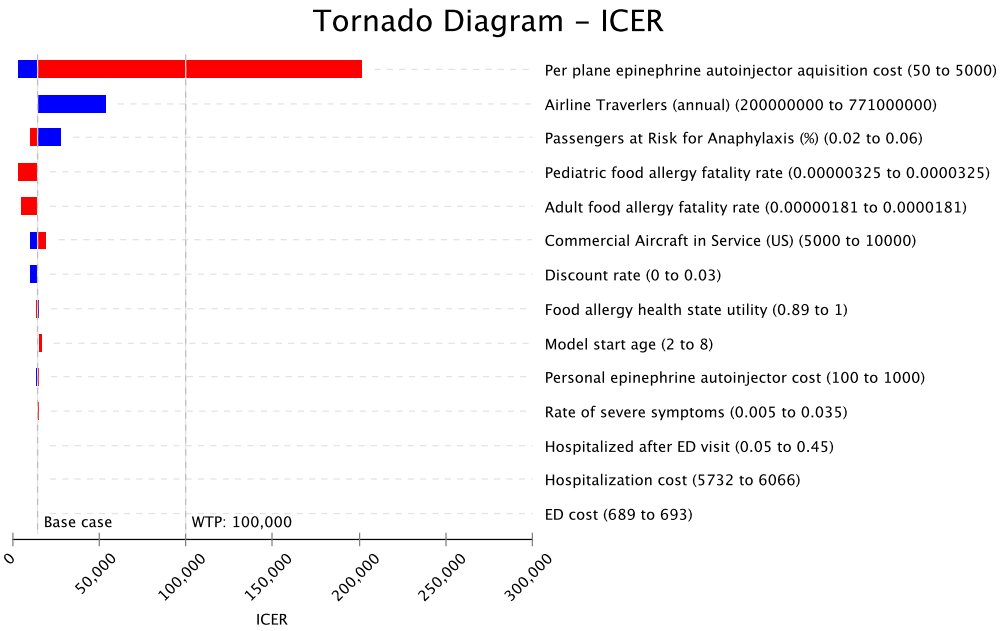


FIGURE 3. Tornado diagrams of deterministic sensitivity analyses. Analyses shown for the supplemental airline epinephrine autoinjector vs no autoinjector. Blue bars represent assumptions and levels below the base model and red bars represent assumptions above the base-case model. *ED*, Emergency department; *ICER*, incremental cost-effectiveness ratio; *WTP*, willingness to pay.

under accepted cost-thresholds for medical interventions in the United States and the United Kingdom.[31]

The fact that this intervention is cost-effective is somewhat surprising, considering multiple prior cost-effectiveness analyses of epinephrine autoinjectors have actually demonstrated significant opportunity for wasted expense, given variation in costs of commercial products.[18] Studies that have demonstrated cost-effectiveness have done so from paradigms of epinephrine access that leverage epinephrine autoinjectors as a shared emergency resource (similar to automatic external defibrillators) in the public setting, as opposed to tethering use to a "one patient, one twin-pack" paradigm.[9,10] There is evidence that shows parents do support epinephrine device sharing.[32] Part of the other issue in evaluating cost-effectiveness of epinephrine autoinjectors or their clinical guidelines for use is that fatality is often the key outcome, though fatality is a very rare outcome for anaphylaxis, and the absolute degree to which device use actually lowers fatality risk (compared with not using a device) is unknown.[7,33,34] This analysis shows that even at a marginal fatality risk reduction estimated to be as low as 1.4%, stock airline autoinjectors are cost-effective within the same acquisition cost as a recently published model of stock pubic school epinephrine autoinjectors.[10] Airline stock epinephrine cost-effectiveness greatly exceeds that of the public school model because the costs can be spread over significantly more at-risk individuals who fly versus attend school (hundreds of millions vs hundreds of thousands) from a societal perspective, and this greater number of covered lives by the device provides the device more value in terms of its cost, even acquiring a new device per aircraft each year. Training costs are not known with certainty—ample sources of free, online training courses exist that can reliably train someone to use an autoinjector. Such training could be incorporated into routine training provided to flight crews regarding using standard onboard medical equipment, such as an oxygen canister and nonrebreather mask or automatic external defibrillator. However, even with additional educational costs modeled, a supplemental autoinjector strategy is cost-effective.

Although the supplemental model is certainly cost-effective, up to even very high device cost ceilings, the larger question of the necessity of having this form of epinephrine on a commercial aircraft is worth considering. Epinephrine ampules themselves are available at exceptionally low costs, and most hospitals and allergy practices use this form for anaphylactic emergencies as opposed to an autoinjector. Although data do exist to show that laypersons can and do struggle to draw the right epinephrine dose quickly from an ampule with a needle and syringe compared with an autoinjector,[27,28] it is unknown how often the on-board source epinephrine is needed for an in-flight allergic emergency, given the rarity of in-flight anaphylaxis. However, the likelihood that someone with a known condition placing them at risk for anaphylaxis would fail to have their own epinephrine autoinjector with them is not insignificant, as many individuals at risk for anaphylaxis who are prescribed epinephrine fail to have it available when needed.[21,35] Such issues of necessity and degree of anticipated use will likely factor in to any FAA or individual airline decision to supplement or outright swap epinephrine forms in their emergency medical kits, and additional legislation may be needed to ensure compliance. However, this simulation is not designed to evaluate this question, and only answers important questions pertaining to the cost and cost-effectiveness of such actions.

Limitations to the present analysis include difficulty in modeling in-flight food allergy or other causes of anaphylaxis fatalities. Food allergy is the most likely in-flight cause of anaphylaxis given the population prevalence of food allergy, and the commonality of food service on an aircraft.[25] Although the model based food allergy fatalities on annual published food allergy fatality rates,[17] applying specific rates to in-flight fatality is limited by this outcome being a rare occurrence, lack of published literature on the topic (because of it being so rare), and instability in the effect estimate. To account for this uncertainty, the model assumed a 10% risk reduction in the annual food allergy fatality rate of passengers traveling with food allergies; however, the actual risk reduction may be lower or higher, which was accounted for in sensitivity analysis. Importantly, sensitivity analysis demonstrated that even a minimal risk reduction of 1.4% for the strategy of supplemental airline epinephrine would be cost-effective, which likely renders this limitation moot. The base model assumed 771 million US travelers annually;[13] as noted in the Methods section, this is a measure of total persons enplaning, and not the unique number of passengers, which may be lower. Risk was modeled per individual passenger on an individual flight, given that a device would not follow a passenger but would statically remain on an aircraft. Given that some passengers will travel on multiple flights per year, sensitivity analyses were performed to model 200 million unique airline passengers each year, with simulations still demonstrating supplemental airline epinephrine autoinjectors to be cost-effective. Stock airline epinephrine autoinjectors were still cost-effective even when assuming a more conservative estimate that 52%[22] of the US population has flown at least once in the past year. Only when a low assumption of unique travelers per year was combined with a 2% passenger risk for anaphylaxis, did the ICER of the supplemental autoinjector strategy exceed $100,00/QALY and cease being cost-effective. However, it is more likely that the number of passengers at risk may be greater than the 4% base model assumption, because passengers with anaphylaxis from non—food-allergic causes would also benefit from undesignated stock airline epinephrine. We do not know the cost of acquiring a medical kit from whichever vendor the US air carriers use, or know what a device company would contract with an airline to provide such devices. However, we show that even at the current retail price of approximately $700 for a twin-pack, the supplemental model would be cost-effective. We operated under the assumption that removal of epinephrine ampules (a cheap source of epinephrine)[36] in the present kits has a negligible effect on the kit price, and therefore did not model a replacement model where only autoinjector devices are included in the medical kit. Lastly, we did not model the effect of passenger-provided devices that could also be shared in the event of in-flight anaphylaxis.

Epinephrine is a life-saving drug when used to treat anaphylaxis. Autoinjectors have been shown to be easier for laypersons to use compared with drawing epinephrine up with a needle and syringe from an ampule, but such devices cost significantly more. To date, although all airlines are compliant with an FAA mandate to have 1:1000 epinephrine on-board, no US airlines have stocked epinephrine autoinjectors, instead relying on the ampules in standard medical kits. Our analysis shows that supplementing the current on-board medical kits with epinephrine autoinjectors can be a cost-effective strategy that could improve health outcomes at a very reasonable cost, considering the number of at-risk passengers across which acquisition costs could be spread. Airlines and the FAA should consider this

management option and policy, given the devices can provide high value at an exceptionally low per passenger cost.

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