ONLINE APPENDIX

Appendix A. History of Ventilator Innovation

The earliest examples of artificial ventilation stem from domain experts who had specialized knowledge, a pattern that persisted until 2020. These early users and domain experts conducted experiments in the United Kingdom in the 1660s, which showed that artificial ventilation could be used to resuscitate and sustain those who were previously presumed dead (Tobin et al. 2012).

In 1832, the first negative pressure ventilator was developed in Scotland by a physician. The device was an enclosed airtight box in which the patient could sit, with a seal formed around his or her neck. Bellows were placed inside the box, but were operated from the outside (Slutsky 2015; Tobin et al. 2012). Negative pressure is the natural way humans breathe with a vacuum created by the diaphragm and the chest muscle contraction (Wertheim 2020).

Over the next 100 years, scientists, physicians, and engineers iterated and experimented with different negative pressure designs, each user leveraging their specialized knowledge to drive innovation. In 1928, the first iron lung was developed by a physician at Harvard, but it was not until 1931, spurred by a severe polio epidemic, that the design was refined to reduce cost and adopted by companies for use (Kacmarek 2011; Slutsky 2015). Polio is a disease that leaves patients unable to breathe on their own due to the virus's ability to paralyze muscles in the chest (Pontoppidan 2002; Tobin et al. 2012). The redesigned iron lung consisted of a cylinder tank that encased a patient up to the neck and assisted the patient's breathing with a vacuum pump (Wertheim 2020). Even with the reduced cost, iron lungs were cost prohibitive for many health care providers, costing $1,500 per unit, equivalent to the average cost of a home in the United States in the 1930s (Suhy 2020). Negative pressure ventilators (primarily the iron lung sold by manufacturers Emerson and Bird) were the dominant means of ventilation until the 1950s (Pontoppidan 2002; Slutsky 2015; Suhy 2020).

For the last seventy years, significant advancements in ventilation technology have been driven by the pulmonary and critical care experts at Massachusetts General Hospital (MGH). Starting in 1951, there was a shift from negative to positive pressure approaches due to the bulbar polio variant, which led to 80 percent of the affected patients dying comatose in an iron lung ventilator (Lassen 1953). In response to these early outcomes during the Copenhagen polio epidemic, anesthesiology Bjørn Ibsen sought a new approach to treating patients. Ibsen had trained at MGH, where he was taught the bagging method – hand-squeezing a rubber bag while a patient was under anesthesia during surgery. Ibsen introduced the practice to the Blegdam Hospital and had nearly 1,500 students providing manual ventilation by squeezing bags to patients around the clock. The results were nearly immediate, as mortality rate fell from 80 to 50 percent in one week, to 23 percent four months later (Lassen 1953; Tobin et al. 2012). Ibsen's invention, a self-inflating bag, a result of user innovation, is still used today; furthermore, the invention validated the need for practical mechanical ventilators and established the modern intensive-care unit, where acutely-ill patients are grouped together for treatment (Slutsky 2015; Tobin et al. 2012). After the 1951 polio epidemic, the use of the positive pressure mechanical ventilation became the standard treatment for patients. In 1976, the Food and Drug Administration (FDA), charged with regulating the safety and efficacy of medical devices, classified ventilators as Class III devices (Tobin et al. 2012).

MGH has continued to be a leader in advancements in pulmonary care, by contributing their expertise to the four generations of advancements in positive pressure ventilators have occurred through closed innovation and have been expert-driven; however, in the 1950s there was a shift from user innovation, to companies becoming primary sources of innovation. In the 1950s, first generation positive pressure mechanical ventilators could only provide volume-controlled ventilation, as patient-triggered ventilation was not yet available. These ventilators had pistons, and did not have alarms, specific settings, or monitors (Kacmarek 2011; Slutsky 2015). One of the earliest positive pressure mechanical ventilators was the Bang Ventilator that was a direct result of the experiences in Copenhagen; however, at the time, volume ventilators were cost prohibitive and rarely used in the United States (Pontoppidan 2002).

Starting in the mid-1970s, second generation, patient-triggered ventilation with monitors and basic alarms emerged (Kacmarek 2011). Alarms were added to address fears of patients being accidentally disconnected from machines (Tobin et al. 2012). This generation of ventilators also introduced intermittent mandatory ventilation (IMV), a mode that aids in the weaning of patients off of

the ventilator (Kacmarek 2011; Tobin et al. 2012). This generation only lasted a short period of time as the early 1980's saw the introduction of the microprocessor (Kacmarek 2011; Slutsky 2015).

The third generation of ventilators allowed for a more responsive machine that almost any approach to gas delivery was possible (Slutsky 2015). In addition to more alarms monitoring for patient safety and device performance , these devices were the first generation of machines that used airway pressure release ventilation (Kacmarek 2011; Slutsky 2015).

The fourth generation of ventilators started in the late 1990s and continues to the present day. In this generation, ventilators became more versatile, as additional modes were included (Slutsky 2015). By the 1990s, the innovation and production of ventilators was run by a few dominant actors, with 10 large companies producing ventilators to meet global demand, including Philips, Medtronic, Draeger, and GE Healthcare. The sophistication of these devices, with high R&D costs, additional operating modes, proprietary components, and long regulatory review processes, resulted in the average cost of a ventilator ranging from $10,000 to $60,000.

The Global Ventilator Shortage Problem During the COVID-19 Pandemic

In March 2020, the demand for ventilators—the last line of defense for patients experiencing respiratory failure—became more critical than ever as the number of people who contracted the infection, were hospitalized, and placed into critical care environments grew daily (Iyengar et al. 2020). The shortage of ventilators crossed geographic boundaries, impacting the healthcare system globally, as both developed and developing countries struggled to meet new demands. In the United States, it was estimated that there was a demand of 960,000 ventilators to treat COVID-19 patients, while only 170,000 were available (Ranney et al. 2020). In developing countries, the ventilator shortage had been an ongoing problem for decades (Mantena et al. 2020). In response, countries looked to maximize in-country resources; by late March, 54 governments placed 46 export curbs on medical supplies, including ventilators (Evenett 2020). Limiting trade meant that companies producing ventilators would no longer be able to send them abroad, slowing down or stalling ventilator production (Evenett 2020). This limitation forced able countries, like the United States (U.S.), to address the shortage problem by building their own national stockpiles (Kaliya-Perumal et al. 2020).

In 2006, the U.S. government established the Biomedical Advanced Research and Development Authority (BARDA) within the Department of Health and Human Services (HHS) to prepare medical responses to chemical, biological, and nuclear threats as well as pandemic influenza and emerging infectious diseases. In 2008, after estimating that an additional 70,000 ventilators would be required in a moderate influenza pandemic, BARDA requested proposals from companies to design and build low-cost ventilators that could be quickly produced and widely distributed in emergencies. In 2010, BARDA and Newport Medical Instruments (a company specializing in ventilator production) signed a $6.4 million contract. The U.S. government would buy as many as 40,000 new ventilators from Newport and add them to the national stockpile. In 2011, Newport produced three working prototypes for review and was on schedule to file them for approval in 2013. However, the aim to develop inexpensive portable ventilators became deprioritized when Covidien, a large medical device manufacturer, acquired Newport for $108 million in 2012. In 2014, with no ventilators added to the stockpile, Covidien asked to vacate the contract, as the project was not sufficiently profitable for the company. As a result, in 2014, BARDA awarded a separate $13.8 million contract to Philips—the giant Dutch company with top-quality engineering and expertise in ventilation technology—to create a low-cost, portable ventilator that any health care provider, regardless of their experience in respiratory support care, could use. In 2019, Philips obtained approval from the FDA on a prototype, and HHS ordered 10,000 units (at a cost of $3,280 per ventilator) to be delivered by August 2020. However, as of May 2020, not a single Philips-produced ventilator had been added to the national stockpile; instead, Philips sold two higher-priced commercial versions of the approved ventilator, leading to an investigation by the U.S. House Subcommittee on Economic and Consumer Policy.

To meet the critical need for ventilators in the midst of the COVID-19 pandemic, the U.S. government activated the Defense Production Act, which compels manufacturers to mass-produce goods

that are in high demand and low supply under a federal contract. The US issued the Defense Production Act and delivered costly federal contracts with Philips and other leading ventilator manufacturers. Countries in Europe also issued large contracts to companies like Dräger in Germany and Siare Engineering in Italy, as there were not enough ventilators for the present pandemic. In May 2020, the Trump administration set a goal of producing 181,000 new ventilators in 100 days and called on automakers such as General Motors, Ford, and Tesla to repurpose their factories for ventilator production. Automakers collaborated with existing ventilator producers to meet the new goal. In total, nine contracts were awarded by the federal government, with two contacts, Ford and General Electric, and GM and Ventec Life Systems, accounting for 44% of the total order. The collaboration between GM and Ventec Life Systems yielded successful results, as they delivered on schedule; conversely, production was estimated to take much longer with other producers, as changing existing production processes and sourcing materials to manufacture an entirely different product would require hefty adjustments. Together, GM and Ventec produced a scaled-down version of Ventec's primary machine, the VOCSN. The VOCSN is a multi-function medical device that consists of five systems, one being ventilation. The device was designed to streamline five therapies (ventilation, oxygen, couch assist, suction and nebulizer) into one, portable device. The VOCSN is priced at $21,000 per unit. In response to the demand for ventilators, Ventec produced a simplified version of the VOCSN device, called the V+Pro Critical Care Ventilator. Similar to the VOCSON, its functionality included ventilation, oxygen, and nebulizer therapies. The V+Pro Critical Care Ventilator received emergency use authorization by the FDA on April 7, 2020, seven days after the National Defense Act was activated. The per unit cost of the V+Pro Critical Care Ventilator was $16,300. The collaboration between GM and Ventec yielded 30,000 ventilators in 154 days. As of September 2020, nearly all of the 181,000 ventilators contracted by the federal government had been delivered.

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Appendix B. Estimated number of ventilators in Africa as of April 17, 2020

Country	Number of Ventilators	Persons per ventilator
Somalia	0	-
DR Congo	5	20,356,053
Mali	3	6,517,799
Madagascar	6	4,492,623
South Sudan	4	2,640,311
Central African Republic	3	1,996,952
Burkina Faso	11	1,894,127
Nigeria	169	1,266,440
Malawi	17	1,246,861
Niger	20	1,138,618
Burundi	12	988,818
Zimbabwe	16	909,145
Mozambique	34	885,241
Senegal	20	786,818
Uganda	55	786,418
Liberia	7	724,757
Sudan	80	569,519
Sierra Leone	13	509,610
Namibia	10	263,007
Kenya	259	206,672
Ethiopia	557	194,099
Ghana	200	146,701
Libya	350	19,687

Source: Maclean, R., & Marks , S. (2020, April 18). 10 African Countries Have No Ventilators. That's Only Part of the Problem. *New York Times*. Retrieved July 12, 2022, from https://www.nytimes.com/2020/04/18/world/africa/africa-coronavirus-ventilators.html.

Appendix C. Product Functionality Requirements

	Description	Identifier	Inputs (Requirements)	Module Allocation
General Performance	Modes of Operation	SR-01	Mandatory Ventilation (Primary function / minimum)	Control Module
		SR-02	Spontaneous Ventilation (Secondary function / design goal)	Control, Monitoring Module
	Control	SR-03	Volume Control (Primary function / minimum)	Control Module
		SR-04	Pressure Control (Secondary function / design goal) 5-60 +/- 5 cmH2O	Control Module
		SR-05	Pressure Support 10-15+/-5 cmH2O; may be either flow- or pressure-triggered (Secondary function / design goal)	Control Module
		SR-06	Apnea back-up kicks in at 30 or 60 seconds (+/-5sec) (Secondary function / design goal)	Control, Monitoring Module
	Flow Rate	SR-07	> 60 liters per minute	Drive Module
	PEEP	SR-08	Pressure: 5-15 cmH2O in increments of 5 cmH20 (+/-5 cmH2O)	Control Module
	Inspiratory : Expiratory (I:E) Ratio	SR-09	Mandatory Ventilation: 1:2, 1:3, and 1:4 options available (click-stop)	Control Module
	Respiratory Rate	SR-10	10-30 breaths per minute in increments of 2 bpm	Control Module
	Tidal Volume	SR-11	Option #1: Input height and gender for 6cc/kg TV (+/- 10% or 10mL) Option #2: 350cc (for average woman) and 450cc (for average man) (+/- 10% or 10mL) Option #3: 400cc only (+/- 10% or 10mL) Option #4: 300-600cc adjustable in 100cc increments (+/- 10% or 10mL)	Control Module
Gas	Gas Connectors	SR-12	Compatible with high pressure (~50psi) gas source (i.e., pipeline supply) OR low-flow inlet	Air-Oxygen Mixing Module
	Oxygen delivery	SR-13	Option #1: FiO2 (21%+10%, 50%+/- 10%, 100% -10%) Option #2: adjustable between room air (21%) and 100% (+/-10%)	Control Module

	Description	Identifier	Inputs (Requirements)	Module Allocation
Infection Control	Reusability	SR-15	All components coming in contact with the patients breath must be disposable OR sterilizable (e.g., autoclavable)	Breathing Circuit
	Viral Filters	SR-16	0.22um or smaller filter on patient inspiration and expiration pathway	Breathing Circuit
		SR-17	Ventilator inlet gas to allow filtration	Air-Oxygen Mixing Module
	Cleanable	SR-18	All external surfaces must not degrade with application of standard agents for disinfection (e.g. bleach solution)	All reusable touchpoints
Alarms & Monitoring	Critical	SR-19	Inlet Gas (O2) or Power supply failure	Alarm, Air-Oxygen Mixing, and Power Source Modules

		SR-20	• Inspiratory airway pressure exceeded limits
			  • Pplat <30-35 cmH2O
			  • Peak P no more than 2 cmH2O greater than Pplat
			  • Fail-safe valve opens at 60cmH2O (powered or un-powered)
				Alarm and Monitoring Modules

		SR-21	Apnea (i.e. patient not breathing) on spontaneous mode (secondary)	Alarm and Monitoring Modules
		SR-22	Inspiratory and PEEP pressure not achieved (i.e. disconnection)	Alarm and Monitoring Modules
		SR-23	Tidal volume not achieved or exceeded (with ~20% tolerance)	Alarm and Monitoring Modules
		SR-24	O2 disconnection	Alarm and Air-Oxygen Mixing Modules
		SR-25	Alarm Volume 60 to 80 dBA at one meter (+/- 5 dBA)	Alarm Module
	Monitoring	SR-26	Actual Value (TV, RR, PEEP, FiO2, Flow Rate, PIP)	Monitoring Module

	Description	Identifier	Inputs (Requirements)	Module Allocation
Ventilator Specific Standards / Misc.	Ventilator Specific	SR-27	Vent performance for </=10,000 ft Altitude,	Guidance provided in Round 2
		SR-28	Durability =2,000 hours	Guidance provided in Round 2
		SR-29	Compatibility with readily available patient circuits, (ISO 5356-1 fittings)	Guidance provided in Round 2
		SR-30	Comply with FDA Ventilator Guidance Standards (i.e. ISO 80601-2-12)	Guidance provided in Round 2
	Medical Device Generic	SR-31	Comply with general Medical Device Guidance Standards (e.g. ISO 13485, ISO 14971, ISO 62304, ISO 62366)	Guidance provided in Round 2
Electric (if applicable)	Power	SR-32	120VAC	Power Module
	Electrical Safety	SR-33	Comply with IEC 60601-1 and IEC 60601-1-2	Guidance provided in Round 2
	Battery Backup	SR-34	None with labeling (primary function)	Power Module
		SR-35	1 hour (secondary function / design goal)	Power Module

Appendix D. CoVent-19 Projects' Design Files and Demo Videos

Project	Design Files	Demo Video Link
SmithVent	https://grabcad.com/library/smithvent-1	https://www.youtube.com/watch?v=XMoux1WhgNg&ab_channel=SmithVent
Vox	https://grabcad.com/library/invent-pneumatic-ventilator-1	https://www.youtube.com/watch?v=NPPmvzpgrWo&ab_channel=Jayati.design
Respiraworks	https://github.com/RespiraWorks/Ventilator	https://www.youtube.com/watch?v=GZNyYIwBEb8&ab_channel=EdwinChiu
Baxter Ventilator	https://grabcad.com/library/baxter-ventilator-1	N/A
CoreVent	https://grabcad.com/library/core-vent-1	N/A
Lung Evolve	https://grabcad.com/library/lung-evolve-1	https://www.youtube.com/watch?v=rqqTsOJ4_Do&ab_channel=LungEvolve
Op Vent	https://grabcad.com/library/op-vent-1	https://www.youtube.com/watch?v=vAR43ow1w0Q&ab_channel=OPVent

Appendix E. Ventilator Classification Tiers

Tier	Description
Tier 1: Intensive Care Unit (ICU) Ventilators	ICU ventilators are high-end devices that include the sophisticated diagnostic measurements necessary to care for patients with mild-to-severe lung disease. The biomedical integration into the alarm system and electronic medical record (EMR) is often seamless. These are the most ideal ventilators for Acute respiratory distress syndrome regardless of cause, including COVID-19. These machines require specialized training, equipment, and multiple personnel to run effectively and efficiently. They are expensive to purchase and maintain and require continuous power and oxygen sources.
Tier 2: Transport Ventilators	Transport ventilators are easily stored when not in use. Their compact size simplifies resource sharing. Most models now have expanded options for diagnostic measurements, available modes, and patient triggering. The device integration is not as robust as other models with regards to EMR and alarms. Most transport ventilators require intensive training and medical expertise. These ventilators also have batteries so they can be used without a continuous power source.
Tier 3: Battlefield Ventilators	A subset of transport ventilators, battlefield ventilators were designed to be easy to use, sturdy, and usable in austere environments with minimal medical training. These ventilators should be considered when rapid expansion requires the use of minimally trained clinicians. These ventilators also have battery power and thus do not require a continuous power source.
Tier 4: Anesthesia Ventilators	Anesthesia machines can operated as a ventilator. Unfortunately, they require expertise above and beyond ICU ventilators. Since these machines are designed for administering anesthesia in operating rooms, they require the expertise of an anesthesia-trained clinician. The operation, maintenance, and use of these ventilators differ from traditional models; as such, a clinician trained on other ventilators will not be able to operate them safely. Anesthesia ventilators also require a regular oxygen and power source and do not have all the sophisticated diagnostics of other ventilators. Lastly, they do not integrate well with alarms and EMRs.
Tier 5: Home Ventilators	Home ventilators are used largely for patients with normal lung function but impaired control of breathing who do not require high oxygen delivery. These oxygen specifications represent a large drawback of using home care ventilators for hypoxemic respiratory failure related to ARDS, as many patients with ARDS require higher amounts of supplemental oxygen support. The device integration for alarm monitoring is minimal. Additionally, many of these ventilators only have a few basic modes of operation. These ventilators are easy to learn and use, as many non-medical individuals can operate them with minimal training.
Tier 6: Novel Ventilators	In dire circumstances with no other options, manual bag-valve mask squeezers and other novel ventilators could be deployed for use. Unfortunately, coupling a simplistic approach of ventilation with typical alarms for safe mechanical ventilation is problematic. Their use should be short term and with significant clinician oversight, as these machines will not work for the majority of critically ill patients.

Note: This framework has been developed by Drs. Jarone Lee, Carolyn LaVita, and Julian Goldman at Massachusetts General Hospital for ventilators available on the market.