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Respiratory protection against airborne pathogens is crucial for pandemic/epidemic preparedness in the context of personal protection, healthcare systems, and governance. We expect that the development of technologies that overcome the existing challenges in current respiratory protective devices will lead to a timely and effective response to the next outbreak.

Role of Respiratory Protection in Pandemic and Epidemic Preparedness

Influenza, a major respiratory disease, poses great risks to global health. Influenza epidemics and pandemics are responsible for 250 000–500 000 deaths each year (www.who.int/mediacentre/factsheets/fs211/en/) and >50 million fatalities worldwide in the past century (www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html), respectively. The next influenza pandemic is estimated to cause ~60 million deaths [1]. Ideally, vaccination within 2 months of the outbreak can provide effective protection [2]. However, because several months are necessary for vaccine development and administration, the infection risk is heightened during the non-vaccine period. This is further supported by the outcomes of 2002–2003 severe acute respiratory syndrome (SARS) outbreak that originated in China, in which the disease was transmitted globally within few weeks, but the first vaccine Phase I clinical study began a year after the outbreak [3]. Logistically, an effective pandemic preparedness plan should include both vaccination and alternative mitigation methods (pharmaceutical – antiviral; non-pharmaceutical – isolation, administrative control, personal protective measures). Therefore, respiratory protection devices are a key non-pharmaceutical intervention that is essential to the global strategy for pandemic readiness.

The parameters behind respiratory protection and airborne transmission intertwine in a complex system that can be broken down into four bidirectional components: (i) release, (ii) infection, (iii) filtration, and (iv) protection (Figure 1). Once a subject is infected, nanometer-to-millimeter-sized pathogenic particles can be released while breathing, speaking, sneezing, or coughing, and infect a host respiratory tract via different mechanisms that depend on the aerodynamic size of the particles (d₄₃ < 5 μm, lower respiratory tract; 5 < d₄₃ < 100 μm, upper respiratory tract). Similarly to infection, current respiratory protection devices filter infectious particles in a size-dependent manner. Filtration efficiency, comfort (e.g., breathability), and fit at the face-mask interface govern technical performance. While effective management and availability of control measures are crucial to an outbreak response, the pathogens (virus/bacteria/fungi) captured on filters are an intrinsic concern because of fear of cross-infection, new aerosol release, and contaminated waste.

Recurrent recommendations regarding respiratory protective measures by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) emphasize their prominent role in emergency preparedness. Nonetheless, fewer scientific efforts have been focused on respiratory protection technologies compared to vaccine development technologies. We present here an overview of currently available respiratory intervention technologies and their implications for future research directions in response to pandemic/epidemic outbreaks.

Limitations of Current Technologies

Surgical masks have been in use for over 100 years as barriers against the development of infection via large droplets produced during surgery. N95 filtering facepiece respirators (N95 respirators) were introduced in 1995 as part of the National Institute for Occupational Safety and Health (NIOSH) 42 Code of Federal Regulations (CFR) Part 84 on non-powered air-purifying respirators (www.cdc.gov/niosh/npt3/topics/respirators/pt84abs2.html). Currently, surgical masks and N95 respirators are the two main intervention measures for personal respiratory protection. Nonetheless, technical challenges exist, some of which are shared by both devices: (i) filtration

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A primary issue concerning the efficacy of surgical masks against airborne pathogens is low filtration efficiency. Although performance can vary drastically among models, inconsistent reports on surgical mask efficacy are probably associated with improper application, resulting in performance mismatch. Another crucial issue is cross-infection/transmission. Because viruses and microorganisms can survive for at least a few hours to several days [4], masks and respirators become a source of infection for the wearer and others, thus limiting them to single use. Infectious aerosols on filters can also be re-released into the environment (i.e., re-aerosolization), for example through accidents. With a particle diameter of 1.15 μm, re-aerosolization from N95 respirators as a result of a fall (drop height, 0.76 m) was between 0.002% and 0.012% [5]. Various sterilization methods (e.g., ethylene oxide, formalin, UV, bleach, hydrogen peroxide) have been tested to recycle respirators. However, the drawbacks of each method, such as performance deterioration and generation of toxic residues, have restricted their application. As an example, decontamination of N95 respirators by autoclave, 160 °C dry heat, 70% isopropanol, and soap and water lowered the filtration efficiency [6]. Ethylene oxide treatment of respirators caused deposition of hazardous residues of 2-hydroxyethyl acetate on the straps, and bleach, oxidants, or dimethyldioxirane raised issues of sharp odor and incompatibility with staples/nosepiece [7]. Despite the need for further research, with safety as a preponderant concern, mask recyclability would be beneficial because it would reduce the amount of biohazardous waste and derived risks. In addition, reusability would naturally address a shortage of respirators during pandemics.

Furthermore, aerosols penetrate through loose-fitting masks/respirators, based on wearer facial features, movement, proper and timely fitting/check, aerosol size, and mask shape. Particles < 10 μm enter through faceleaks 5–6-fold and up to 10-fold more than through the filter of surgical masks and N95 respirators, respectively [8]. Thus, although improving filtration efficiency is necessary, better fitting should be a primary objective to fully address aerosol penetration.

Interestingly, the general public tends to disregard infection control guidelines. As such, although respirators are recommended when airborne transmission is possible, surgical masks have experienced greater acceptance because of advantages such as comfort, availability, and cost. However, inappropriate application of devices may not provide consistent protection. This in turn stimulates research and development of new technologies to close the gap between guideline and practice.

How Can We Move Towards Safer and More Effective Respiratory Protection for a Timely Emergency Response?

Diverse methods have been investigated to improve the performance of respiratory protection devices (Box 1), such as higher
filtration efficiency without sacrificing breathability. Representative examples include fabrication using nanofibers and incorporation of electric charge by plasma treatment and charge-carrying agents. However, major technical challenges remain to be addressed for effective preparedness from the standpoint of contamination and infrastructure. Hence, production of a filter that inactivates the collected pathogens would bring key improvements to current surgical masks and respirators, resulting in increased protection, reduced risk of cross-infection, and recyclability without decontamination (Figure 1).

To inactivate viruses, antimicrobial treatments have been investigated for filters utilizing halogens, metals, quaternary ammonium compounds, antibody–antigen reaction, and salt recrystallization. Chlorine compounds such as N-halamines and iodine-treated filters have been assessed against bacteria (Micrococcus luteus and Escherichia coli) [9]. In addition, surgical masks functionalized with silver nitrate nanoparticles or quaternary ammonium inactivated bacteria (Escherichia coli and Staphylococcus aureus, and Acinetobacter baumannii, Enterococcus faecalis, and Staphylococcus aureus, respectively) by interaction with thiol groups (100% reduction in ~48 h) and membrane permeability damage (~92% reduction in 1 h), respectively [10,11]. However, antimicrobial technologies based on silver/copper, reactive oxygen molecules, iodine, and titanium dioxide did not exhibit inactivation properties against MS2 virus [12]. Another approach to inhibit virus transmission involves modification of the filter surface with the antigen-specific antibodies [13]. Despite the merits of each approach, effective protection against virus aerosols is still limited by slow action (rapid inactivation should occur in the order of minutes, not hours) or binding specificity. Recently, salt recrystallization was found to physically destroy viruses on surgical mask filters within few minutes in a strain-independent manner, potentially enabling reuse without separate processing steps [14]. Notably, most studies have focused on the functionalization of the outermost and middle layers of the mask. The design of the protection device layers should consider the spatial deposition of aerosols within masks and their contact surface.

Based on the above observations, we identify three central parameters in developing pathogen-inactivating filters. First, an inactivation mechanism should act rapidly to avoid cross-infection. Although additional aspects are involved (e.g., fraction of transferred pathogens, surface area), unsafe handling and people’s tendency to touch their face every ~4 minutes lead to a risk of contact transmission from a pathogen-laden mask/respirator [15]. Second, pathogens should be neutralized in a strain-nonspecific way. The pathogen/strain responsible for the next pandemic cannot be exactly predicted because of continuous mutation. As such, antibody-functionalized protective devices that target a strain-specific virus would delay the emergency response. Thus, the pathogen-killing mechanism should guarantee broad-spectrum protection. Third, the ideal technology should be

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**Box 1. Performance of Respiratory Protection**

The key technical components of the performance of current respiratory protection devices are filtration efficiency, fit, and comfort. Each has a significant role in protective efficacy, and specific parameters can be tuned to improve them.

**Fit:** non-filtered air entering through a poor seal between mask and face is a prominent concern. Efforts towards reducing face leaks can be grouped as follows.

(i) Material selection that allows customizable mask shape/tightness.

(ii) Investigation of wearers’ facial features, and simulation of the spatial distribution of leaks to guide mask design.

(iii) Fit testing/training optimization to increase efficacy/compliance.

**Filtration efficiency:** whereas N95 respirators have a certified filtration efficiency of 95%, surgical masks have low performance. Several major parameters can be controlled to decrease particle penetration.

(i) Decreasing the diameter of fibers.

(ii) Decreasing the size of filter pores.

(iii) Controlling fiber electrical charge through manufacturing process/material selection.

(iv) Increasing the thickness of the filters.

**User comfort:** the wearer’s perception of comfort is crucial to correct practices and effective protection. Tolerability during mask use is often limited by the following factors.

(i) Reduced breathability caused by pressure drop across the mask.

(ii) Heat build-up inside the mask because of reduced air exchange while breathing and lowered heat convection from the face.

(iii) Carbon dioxide rebreathing.

(iv) Discomfort from prolonged contact between skin and rough materials.

(v) Difficulty in communicating.
Concluding Remarks and Future Perspectives

The unpredictable nature of airborne pandemic diseases and their impact on our economy and society present a big challenge at the national and global level. Only a prompt and coordinated response among different sectors of society can maintain security from this threat, which can be implemented through the help of technological innovations and comprehensive planning. Unfortunately, despite being recognized as a key technical element in pandemic/epidemic preparedness, innovation in the design of respiratory protection devices has been sparse. In alignment with the strategic plan for pandemic/epidemic preparedness, we anticipate that incorporation of efficient pathogen-neutralization mechanisms can overcome the existing technical (contact transmission, source control, waste) and non-technical (supply shortage, policies, cost) challenges in respiratory protection. Thus, we expect this engaging field to expand further, with the promise to offer enhanced protection to the global population.

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Device-Independent Bacterial Biohybrids

The aim of biohybrids is to harness cell motility and energy for user-desired tasks, including the transport of artificial cargo, drug delivery, or to power a tool for micromanipulation of other objects [1, 2]. Bacteria-powered biohybrids (Box 1) present new micromachines to perform complex tasks at the micro- and nanoscale. In vitro, biohybrids have demonstrated the ability to selectively sort particles [3] and even build microarchitectures [4], but real-world applications for bacterial biohybrids have yet to be achieved. However, the biomedical field offers many opportunities to utilize the micromaneuverability and natural sensing capabilities of biohybrids for non-invasive medical applications that are not possible with current technologies, and recent research has been pushing biohybrids towards this goal. Current bacterial biohybrids have the potential to be used for cancer or disease detection, targeted drug release, and even disruption of infectious biofilm sites. However, many challenges with external guidance, cargo loading and unloading, and efficient swimming remain, hindering their use in clinical and therapeutic applications. We present here recent attempts and developments to improve bacterial biohybrid performance and move the field closer to in vivo medical applications.

Bacteria–Particle Swimmers

Bacteria attached to micro- or nanoparticles are some of the best-studied bacterial biohybrid systems. Bacteria adhere to the particle and carry it while swimming, creating an effective cargo delivery system. Guided cell adhesion of the bacterial body to localized regions of the

Bacterial biohybrids use the energy of bacteria to manipulate synthetic materials with the goal of solving biomedical problems at the micro- and nanoscale. We explore current in vitro studies of bacterial biohybrids, the first attempts at in vivo biohybrid research, and problems to be addressed for the future.

Forum

Pushing Bacterial Biohybrids to In Vivo Applications

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Bacterial biohybrids use the energy of bacteria to manipulate synthetic materials with the goal of solving biomedical problems...