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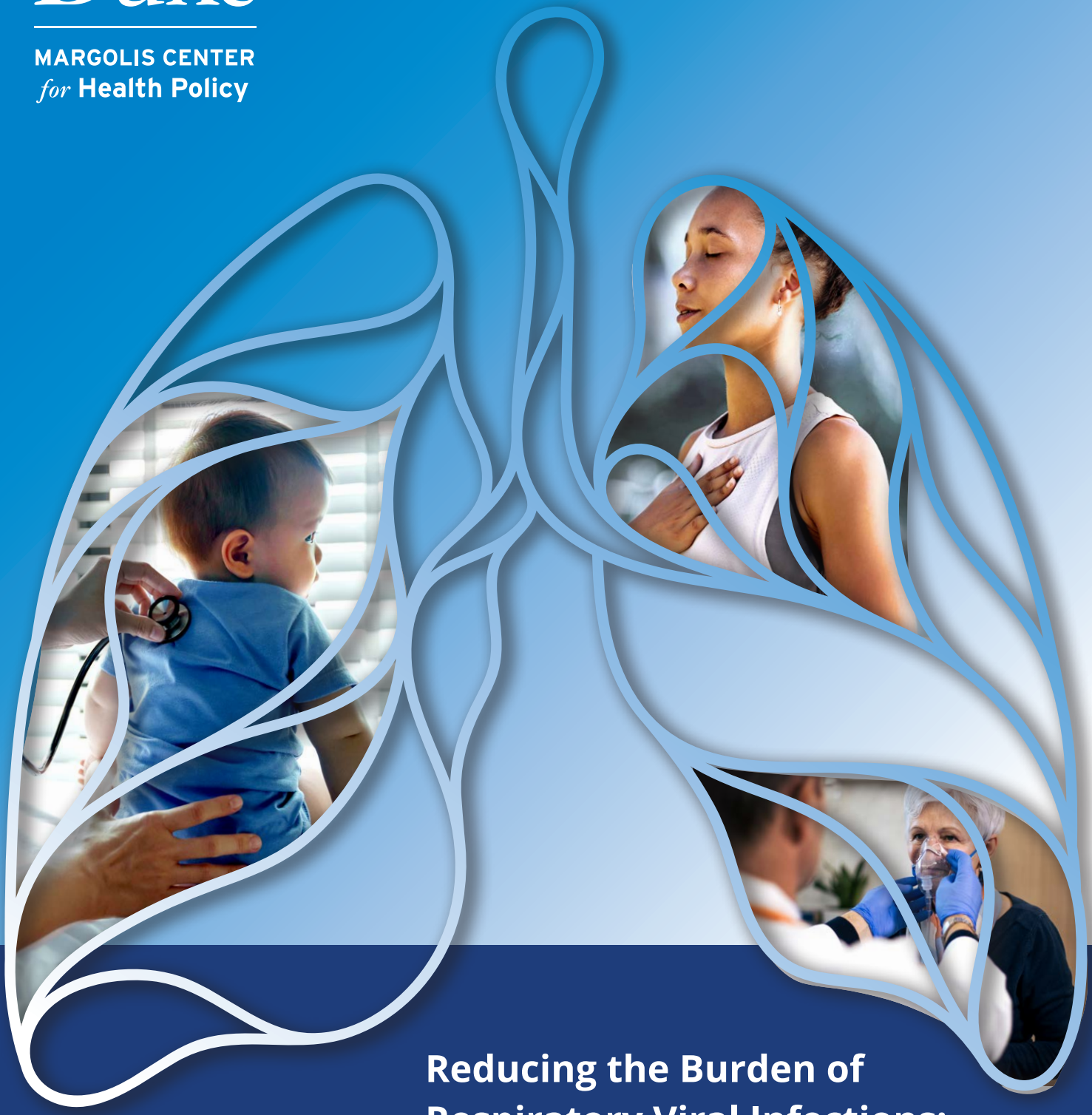

Reducing the Burden of Respiratory Viral Infections: *A Policy Framework to Accelerate Biomedical Innovation to Benefit Population Health*

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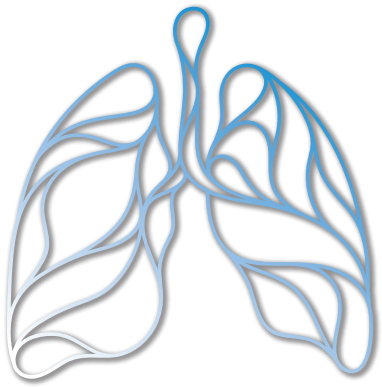

Introduction

Diagnostics, therapeutics, vaccines, and other biomedical technologies are creating unprecedented opportunities to reduce death, disability, and other adverse population health effects from infectious diseases. Over the past few years, important new products have come to market that have the potential to substantially reduce the impact of COVID-19 and Respiratory Syncytial Virus (RSV), as well as help contain influenza. These capabilities benefit individuals who use them by reducing the duration and severity of symptoms, but also benefit people around them by reducing transmission and complications from additional infections. Further biomedical innovations could enable greater progress in containing infectious disease, such as therapies in development that not only prevent severe infection or death, but also hold promise for avoiding contracting and transmitting viral infections. Such treatments have some additional benefits for individuals—e.g., avoiding mild short-term symptoms—but they could also have greater benefits on population health, through a greater impact on transmission that better protects higher-risk contacts in the community. For example, the U.S. government's Project NextGen is currently investing in COVID-19 vaccines and therapies (including potential prophylactic therapies) that could have these benefits.

As we describe below, while the potential benefits of *transmission reduction* for population health have long been recognized, U.S. and global public policies do not have clear, well-developed frameworks for assessing, valuing, and supporting the development and use of biomedical innovations that have such population health impacts above and beyond their benefits and risks for individual health. The U.S. has mandated coverage without copays for certain vaccines and other preventive treatments with strong supporting evidence of benefits. But these evidence assessments—and the associated approval, coverage, and payment policies—are generally focused on *individual benefits* and risks. Indeed, recent US Food and Drug Administration (FDA) guidance on evidence requirements for future COVID-19 vaccines focuses on demonstrating impact on prevention of death and serious complications requiring hospitalization, with less discussion of standards for a further claim related to reducing transmission or infection. Further, as we describe below, there has been little analysis to guide what additional priority, if any, public and private coverage and payment policies should place on treatments that have similar impacts on serious individual outcomes but differ significantly in terms of reducing transmission.

The absence of clear policy guidance on these potentially important biomedical opportunities for reducing transmission has significant public health implications, especially in settings like in the U.S. and many other countries where there is only limited support for vaccine or treatment mandates to contain infections and improve public health. Current regulatory, coverage, and payment policies help encourage use of vaccines and therapies that are safe and effective, but may not fully reflect the potential benefits of more widespread use of products that do more to reduce transmission. Both because some individuals may be more willing to use a product because it is more protective for those at risk around them, and because policy reforms may influence the extent to which such products are used, progress in biomedical innovation is increasing the public health importance of policy steps to support the development and use of products that do more to reduce infection transmission.

An enhanced policy focus on transmission reduction could also result in greater impact of existing diagnostics, therapeutics, and vaccines. Evidence-based policies that encourage greater use of current COVID-19 and flu over-the-counter (OTC), rapid diagnostic tests not only help individuals get treatment to reduce their risk of severe infection; they also can support voluntary changes in behavior like staying home that reduce transmission. The U.S. government has provided limited access to free COVID-19 tests, presumably with both individual and population health benefits in mind. But this has been a short-term policy decision reflecting residual COVID-19 emergency funding, not a systematic policy. Greater voluntary use of respiratory vaccines and therapies with transmission-reducing benefits can similarly improve individual outcomes and contain outbreaks. But current Federal policies involve covering such therapies with traditional copays, at least in private insurance. And while CDC recommendations suggest that millions of Americans should receive COVID-19 boosters, RSV vaccines, and flu vaccines, individual vaccine pricing, coverage, and payment policies are currently on track to result in only a small fraction of that large population being vaccinated.

In this paper, we describe a preliminary policy framework to account more explicitly for the population-level benefits of transmission reduction, with the goal of achieving more effective infectious disease containment. Greater containment is increasingly feasible without mandates by leveraging recent and emerging biomedical technologies.

This framework incorporates key dimensions of population benefits to support policies that explicitly account for the value of transmission reduction *in addition* to individual benefits. We include some examples of policy actions consistent with this framework, and highlight implications of the framework on regulatory, coverage, and payment policies, with an illustrative focus on implications for better reducing or blocking the transmission of major respiratory viruses.

We highlight the following questions related to the potential value of more complete accounting for population health benefits beyond individuals:

- Under what circumstances is a more explicit focus on population benefits of transmission reduction likely to be worthwhile, and what policy steps would be most effective in achieving these benefits?
- How can such benefits best be measured and validated?
- Do current regulatory policies provide a clear pathway for products that block or significantly reduce transmission, even if they have relatively modest or no benefits compared to existing treatments for individuals (e.g., some reduction in mild or any symptoms, but little or no clear impact on more serious outcomes)?
- Do current payment policies fully reflect the transmission reduction benefits, including transmission blocking, beyond a product's impact on the health benefits and safety risks to an individual user of the product?

The paper aims to provide a foundation for **a more systematic approach to developing and using biomedical products that continue to provide important health benefits to individuals, but that – through greater individual use as well as greater impact on transmission reduction – reduce or block disease spread in communities.**

A Framework for Assessing the Individual and Population Level Benefits of Biomedical Products That Prevent Serious Infections – and Reduce Transmission

For FDA approval, a medical product must demonstrate that they are safe and effective for their intended use – that is, the benefits of the product must exceed the risks, based on evidence from well-controlled empirical studies. (For emergency use and accelerated-approval products, empirical or other evidence must show that the expected benefits exceed expected risks, with the expectation that further studies will confirm the benefit-risk results for accelerated-approval products where no alternative treatments are available.) However, as we have noted, a product intended to diagnose, prevent, or treat infectious diseases also has potentially valuable benefits beyond those to the individual using the product. These population health benefits occur through their impact on reducing duration and intensity of infectiousness, or on preventing infection entirely:

- ***Clinical benefits*** from preventing sickness in congregate facilities and other communities at high-risk of severe illness and reducing the use of health care resources so that they are distributed across other illness and disease.
- ***Economic benefits*** from preventing sickness in populations that include workers, which can decrease productivity both directly and indirectly through absenteeism, and the need to care for dependents or other responsibilities that limit time and energy spent working.
- ***Social benefits*** by maintaining and strengthening health and social infrastructures, keeping students and staff in school, improving quality of life at a population-level, and enhancing equity in health care.

A framework for evaluating the individual and population benefits of medical products, and the coverage and payment policies that support their use, would include both the usual individual benefit-risk analysis for assessing biomedical products plus an explicit analysis of **reduction in infection transmission** by users of the product. In this framework, measures of *transmission reduction* could be used to judge the additional population health benefits of individual use, based on experimental or real-world evidence, and validated markers of reduced transmission (e.g., viral load for many infectious diseases, and reduced symptoms for some). Higher measures of transmission reduction would be expected to lead to *transmission blocking* in a greater range of community conditions of use.

In the following sections, we illustrate the implications of this framework for policies related to regulatory approval and labeling, coverage, and payment for products that may reduce or block infection transmission.

Reducing the Burden of Major Respiratory Viral Infections

Recent and future biomedical innovations related to containing major respiratory viral infections illustrate how a population-level framework could make a difference in the impact of these viruses on the health of the U.S. population. The U.S. entered the 2023 fall respiratory virus season with the most comprehensive set of medical products ever for limiting the impact of COVID-19, RSV, and seasonal influenza. These products include diagnostics (including population screening technologies like wastewater screening, OTC tests, PCR tests, genomic tests, and "multiplex" tests), therapeutics, and new vaccines including updated COVID-19 and flu vaccinations and a new RSV vaccination. Coupled with non-pharmaceutical interventions (NPIs), these improved products have helped to prevent, detect, and limit the severe health consequences of infections. But they also help contain the spread of these infectious diseases, benefitting many Americans who do not have ready access to or choose to use these treatments themselves, further mitigating the impact of these infectious diseases.

FDA-approved labels for these products, and public guidance from the Centers for Disease Control and Prevention (CDC), encourage broad population use of all of these products. Recent Federal policy actions have supported access to these treatments aligned with this guidance, with potential benefits for containing infections. With the exception of programs for uninsured and underserved patients, since the end of the COVID-19 Public Health Emergency (PHE), vaccines and therapeutics are largely covered more like traditional, individual-use, fee-for-service products, not products intended to advance both individual and population health.

The U.S. Department of Health and Human Services (HHS) Bridge Access Program and Health Center COVID-19 Therapeutics Program provide free COVID-19 treatments for uninsured and underserved populations, and the Vaccines for Children program provides access to RSV vaccines and therapies for children covered by Medicaid. HHS has also partnered with pharmacy chains and additional community providers to increase access to vaccines and therapeutics. Insurance programs are required to cover these vaccines without copays for all indicated populations. However, only a minority of eligible beneficiaries have used these vaccines. Pricing under private insurance is such that population-wide uptake would be very expensive for payers (e.g., over $20 billion for broad private insurance and Medicare uptake of COVID-19 boosters alone). Federal purchasing programs with lower prices for uninsured and underserved populations are lower, but no-cost availability through current mechanisms has not been sufficient to achieve broad enough access to prevent spread.

In comparison to the last several years, since the end of the recent public health emergency, COVID-19 testing has generally become costlier, with insurers generally not covering rapid OTC tests for COVID-19 or for other respiratory conditions. A limited number of free at-home rapid tests for COVID-19 have been available at times of increased expected outbreaks through the U.S. Postal Service. However, these one-time programs may not be sufficient to achieve broader use in the population.

Regulatory Considerations for Better Population Health Through Transmission Reduction

FDA's regulatory processes for infectious disease product approvals already include a number of considerations related to population health benefits from transmission reduction. Currently approved products generally require sufficient evidence that benefits outweigh risks for the individual using the product. As such, available products are largely focused on reducing infection and infection severity in controlled trials with clinical endpoints measured in treated and untreated individual patients.

This traditional regulatory focus on products with individual benefits provides incentives for the development and use of products that have population health benefits, to the extent that products that are individually safe and effective also contribute to reducing disease transmission to others. There is a precedent for regulatory pathways that consider not only individual benefit and risk, particularly with approval of therapeutics for prophylactic use in individuals at low-risk of severe disease. One example

is the recommended use of prophylactic antivirals for influenza outbreak management in long-term care and post-acute care facilities. Two complementary avenues could further incorporate population-level benefits into the FDA's existing regulatory framework:

- Providing guidance for the explicit assessment of potential population health benefits for relevant infectious disease products, to encourage a more systematic assessment of whether available evidence suggests significant and notable potential impact on risk of contracting and transmitting infection, which could represent significant additional value over available products and practices available to reduce transmission.
- Supporting pre- and post-market assessments of safety and efficacy for population-level benefits, i.e., facilitating clinical studies to directly assess impacts on transmission and rate and severity of cases in the community (potentially with a greater focus on high-risk communities).

Additional evidence assessment and evidence development considerations related to population health would be targeted to products that appear, in the initial assessment, to have the potential for large impacts on likelihood of becoming infected and duration and extent of infectiousness, relative to their impact on more severe symptoms (e.g., inability to go to work, hospitalization, and death).

Further regulatory guidance and evidence development supports are likely to be beneficial when the potential health benefits from transmission reduction are relatively large. If an individual is at relatively low risk of these serious complications but could transmit to higher-risk populations, or if approved vaccines and therapies are available that result in low risk of more severe symptoms, clinical trials and regulatory approval may be challenging. In particular, demonstrating a high level of safety for the individual risk-benefit standard may be costly and time-consuming, even if the product itself appears to have little safety risk. For example, what is the path to regulatory approval for a product that has an impact on surrogate markers of infection transmission, such as duration of mild symptoms or viral loads – and thus a potentially important public health benefit in terms of reducing or blocking transmission – but that appears to have little or no additional benefits compared to existing standards of care with respect to more severe outcomes, such as hospitalization or death?

Coverage and Reimbursement Considerations for Better Population Health Through Transmission Reduction

Coverage and reimbursement pathways also can have a substantial impact on development of and access to medical products to reduce or block transmission, and thereby have substantial population health benefits and avoided costs of medical complications and health system burdens that could justify more generous coverage and payment. For the most part, coverage and payment for products that target respiratory viruses has been characterized by coverage classification in terms of individual preventive benefits. All U.S. payers cover preventive services, including services that U.S. Preventive Services Task Force (USPSTF) determines to have strong supporting evidence (grades A or B) of individual health benefits, and vaccines recommended by the Advisory Committee on Immunization Practices (ACIP). As noted above, products with greater individual benefits may also have larger population health benefits. The U.S. also has mechanisms, such as the Vaccines for Children Fund, to purchase vaccines and other infection prevention treatments (e.g., monoclonal antibodies for RSV prophylaxis in infants) for eligible patients not covered by commercial insurance.

Legislation early in the COVID-19 public health emergency provided for population-level procurement of vaccines, therapeutics, and some diagnostic tests, and also required coverage and payment for administration of these products (and laboratory diagnostic tests) without patient copays. These determinations reflected clear evidence of the infectiousness of the SARS-CoV2 virus and a public policy assessment that minimizing financial barriers to use, and supporting health care providers in

informing patients and providing these products about their easy and low-cost availability, would have significant benefits for reducing infection transmission in addition to the direct benefits for individuals using the products. With the end of the public health emergency, vaccines remain covered without copays for all beneficiaries, but commercial and Medicare coverage has reverted toward the usual cost-sharing arrangements that apply to treatments for individuals. With the exception of vaccine-like coverage for prophylactic monoclonal antibody treatment for newborns and high-risk infants, individually-focused coverage and payment policies also remain in place for diagnostics and treatments for other major respiratory infections. In addition, there are no clear frameworks or guidance for public and private payers that directly and reliably account for the additional value of products that lead to greater population benefits from reduced disease transmission.

Over the past two decades, the Centers for Medicare and Medicaid Services (CMS), states, employers, and private health insurers have implemented a variety of payment reforms intended to strengthen prevention, care coordination and management, and other steps to improve individual and population health. These include adoption of innovative product payment models to increase use of safe and effective vaccines, diagnostics, and therapeutics and alternative payment arrangements that shift provider payments from "fee-for-service" to payments that more directly support improvements in quality of care and outcomes in individuals and populations. These reforms provide a foundation for further steps to support transmission reduction and population health benefits.

Applying the Framework: Realizing Transmission Reduction and Better Population Health through Actionable Policy Reforms

In the remainder of this paper, we illustrate how policies and product development might change by applying our framework for population-level benefits of transmission reduction to policies for approval, coverage, and payment for current and next-generation screening, diagnostic, vaccine and therapeutic products. We illustrate potential policy reforms in Table 1 and 2. We focus on applications related to containing respiratory viruses, but also include examples of how policies have already more generally incorporated a population-benefit approach in some instances—with a focus on how these steps might be developed more systematically, including for current and next-generation products targeting respiratory disease. These steps, implemented effectively, could both achieve valuable population health benefits using current products, and clearer incentives and pathways for the development of next-generation products that have greater population health benefits alongside their individual benefits. They would do so by:

- Establishing scientifically sound development and regulatory population health-based pathways for product developers and regulators.
- Ensuring procurement and public/private coverage pathways to provide testing, treatment, and vaccination at scale.
- Ensuring continued data and evidence development on efficacy of products to inform their deployment and use.

Additional implementation considerations for operationalizing these policy reforms include:

- Federal, state, and local strategies to support access and maximize the adoption of transmission reducing and blocking products, including addressing side effects and public trust for using these products.
- Involvement of leaders in health systems, individual practices, community health centers, patient advocacy, payer organizations, and public health organizations to address access, delivery, and uptake considerations.
- The role of the commercial sector in producing and delivering products on a wide scale.

Table 1 | Regulatory Policy Reforms for a Population-level Framework

Diagnostics	• Leveraging the population health benefits of better diagnostic tests through more robust wastewater surveillance infrastructure with standardized electronic data reporting across stakeholders, pooling, and generalized data from local surveillance efforts • Establishing incentives to adapt diagnostics to public health purposes during disease surges, including through regulatory guidance to support validated use of pooled samples • Fostering innovation with challenge programs modeled after RADx to enhance development, commercialization, and implementation of next-generation diagnostics • Providing subsidies to create a warm-based manufacturing capacity of current and next-generation products
Vaccines and Therapeutics	• Creating a post-market evidence generation infrastructure that incorporates clinical trials with simplified processes and adaptable platform style approaches • Utilizing more traditional randomized controlled trials that have facilitated label expansion for past products • Leveraging enhanced authority by FDA to require post-market studies on transmission reduction

Table 2 | Reimbursement Policy Reforms for a Population-level Framework

Diagnostics	• Establishing differential payment rates for laboratory diagnostic tests that confer population-health benefits • Establishing coverage policies to support the use of multiplex testing in various clinical settings • Utilizing alternative payment arrangements like subscription-based purchasing models to incentivize development and ensure product supply • Facilitating a more robust surveillance infrastructure through payment adjustments for participation in surveillance networks • Developing and aligning on standardized validated outcomes, measures of transmission reduction to capture population-level benefit and inform payer coverage decision making
Vaccines and Therapeutics	• Utilizing value-based payment arrangements to address outstanding evidence questions to support coverage • Incorporating outcome measures that reflect use of products with population health benefits in CMMI models and CMS ACOs • Establishing more comprehensive reimbursement infrastructure that reflects the added value of transmission reducing products • Utilizing bulk purchasing agreements to maintain a steady supply of products

Evidence Development for Population-level Benefits

These policy steps depend on developing better qualitative and quantitative evidence on the population benefits of an intervention across the product lifecycle, which can be challenging. Simply having clearer policy pathways related to infection reduction can encourage investments in developing better evidence. However, prioritizing the development of infrastructure for population-health evidence generation as use cases emerge is critical for a systematic approach for the development and effective use of products.

Past epidemiological work has provided evidence of population-level benefits for vaccines. Retrospective cohorts are often used to understand the risks of disease outbreaks in communities and have demonstrated a reduction in outbreak frequency in areas with higher vaccination rate. Cluster randomized trials can provide more direct evidence that vaccination protects both immunized and nonimmunized residents in a community. Additional approaches have shown that efficacy for vaccines in reducing transmission can be estimated from primary randomized clinical trial data. Both epidemiological data, modeled as contact tracing, and pathogen sequencing have been used in simulations to demonstrate the most accurate methods for obtaining vaccine efficacy to reduce transmission in a clinical trial.

Further methodology on vaccine efficacy against transmission identified the relationship between transmission and viral load through four key assumptions. By fulfilling these four key assumptions, both randomized controlled trials and observational studies could use measurements of viral load to assess the efficacy of vaccines against transmission. The population-level benefits for diagnostic testing have also begun to be identified through observational studies. An assessment of routine COVID-19 diagnostic testing in workplaces during the spread of the Omicron variant, found that rapid antigen tests were not adequate for preventing disease transmission. The Rapid Acceleration of Diagnostics (RADx) initiative is also funding projects to examine the effectiveness of antigen tests with cluster randomized trial designs. Further demonstration of population-level benefits for vaccines and diagnostics, including transmission reduction, will require innovative observational and randomized controlled trials designed to accurately assess relevant outcomes.

In a new evidence generation paradigm, the first goal for most products would be to show favorable individual risk-benefit and validated or promising surrogate markers of population health benefits. Then real-world observational or randomized studies can assess the impact on transmission in high-risk settings. This paradigm would get a product to market with a label indicated for individual benefits plus likely evidence of potential population health benefits, with post-market infrastructure support and guidance to enable label expansion.

For products that demonstrate such benefits, additional evidence generation can shape the impact of enhanced regulatory, coverage, and payment pathways to facilitate transmission reduction and population level benefits. Research can also examine how to best utilize products to reduce transmission. As respiratory viruses continue to evolve and novel viruses emerge, these research methods can assess how policies may need to be modified to best target populations and reduce disease spread.

Policy Reforms for Transmission Reduction to Benefit Population Health

Approval, coverage, reimbursement, and guidance for utilizing products targeting respiratory disease have traditionally revolved around incentives to prevent or reduce the severity of individual infections. However, many products on the market have already shown important population-level benefits from reducing transmission, and stakeholders can build on precedent for regulatory and reimbursement policies to reflect these benefits. Past policy actions provide a foundation for actionable steps to account more systematically for the transmission reduction potential of current and next-generation products with the potential to reduce and block transmission. This section identifies such potential further policy steps, and cross-agency opportunities for alignment to appropriately utilize products to achieve population-level transmission reduction.

Diagnostics

Although diagnostics primarily assist with individual decision-making (such as choosing to stay home after a positive COVID-19 test), individual decisions affect the spread of respiratory illnesses at the population level. Diagnostic tests with more accurate, faster results and enhanced reporting platforms can play a key role in containing disease spread during periods of disease surge through behavioral modification. Additionally, diagnostics that are better designed for population-level screening and surveillance can play a key role in alerting Federal and state agencies and communities to outbreaks and new variants in different geographical areas, enabling more effective responses. Regulatory, reimbursement, and evidence generation reforms can support the use of current and next-generation diagnostics to better contain disease spread and provider greater population-level benefits beyond individual results. In particular, reforms that make approval and coverage clearer for products with benefits beyond individual diagnosis can incentivize development of next-generation products. Guidance on the potential use of surrogate markers (e.g., symptom duration, impact on viral load) for population benefit claims as part of an accelerated approval pathway can form the basis for a pathway to expand the indication of use for diagnostic tests to screening and surveillance.

Reforms to incentivize the development and manufacturing of diagnostics

When looking towards the development of next-generation products with enhanced transmission reducing capacities, stakeholders can build upon experiences in supporting rapid innovation during the COVID-19 pandemic. A program similar to the RADx initiative can be targeted to next-generation products that are expected to help achieve population health improvements beyond what would be expected from greater sensitivity, specificity, and timeliness in current products. This can help nascent companies by helping them navigate the regulatory process (including demonstration of potential or actual population health benefits) and scale up production.

To incentivize development through more reliable coverage processes, CMS and stakeholders can differentiate payment rates for laboratory diagnostic tests that provide population health benefits in addition to their accuracy, ease of use, and other aspects of individual benefit. In addition, coverage policies can clarify under what circumstances OTC tests might be reimbursed. As we have noted, greater use of OTC tests can reduce local spread, and there are alternative policy options for public and private payer coverage and payment for such tests. Finally, CMS can bolster reimbursement around multiplex tests that can lead to more informed behavior modification and greater tracking across multiple pathogens. Ultimately, standardized outcome measures for population-level benefits of diagnostics across the respiratory disease space can support the design of pre-market and post-market studies for more predictable, timely coverage and access pathways.

Reforms that bolster continued manufacturing of diagnostics can help ensure that testing continues to be the first step in reducing disease transmission through behavioral modification and evidence of disease spread. To guarantee a steady supply of products for periods of disease surge, Federal and state agencies can provide manufacturing subsidies to manufacturers of testing platforms that allow them to build warm-base manufacturing capacity outside of public health emergencies. Subsidies should vary across the types of platforms required for testing—platforms for molecular tests used in laboratory settings will be different than those for antigen tests used at the point-of-care. Continued immunity from liability under the PREP Act Declaration, through the end of 2024, is also important to support the development, manufacturing, and distribution of diagnostics for COVID-19 and influenza.

Reforms to enhance diagnostic access and individual reporting

Along with increased development and manufacturing capacities, ensuring access to diagnostic tests will be necessary for higher rates of behavior modification among individuals who test positive, and for more robust reporting among those who test. Reforms to support greater diagnostic use include continuing PHE-era reimbursement flexibilities for CMS coverage of laboratory test ordered by pharmacists. States and the Federal government can also prioritize infrastructure for non-clinical testing sites as seen in the first several years of the COVID-19 pandemic.

In addition to these reforms, stakeholders can incentivize increased use of diagnostics with population-level benefits through enhanced reimbursement frameworks. When approaching reimbursement of OTC diagnostic tests, stakeholders can adapt payment rates for products with enhanced reporting features to reflect the population benefit of contributing results to larger data pools. A more generous reimbursement infrastructure can also incentivize further development of reporting platforms in diagnostic tests. Novel reimbursement infrastructures may be supported by alternative payment arrangements like subscription-based purchasing models for products that demonstrate population-level benefits and can be prioritized in periods of disease surge.

Reforms to facilitate the use of testing for surveillance

Several reforms can support the use of testing products as part of surveillance infrastructure to predict, track, and respond to disease spread. Medicare can support reimbursement for surveillance efforts through payment adjustments related to quality and safety of testing, and participation in local public health surveillance networks (in which only a small fraction of positive lab tests would likely need "reflex" testing) or in state and national surveillance networks like the Influenza-Like Illness Surveillance Network. CMS might also include routine surveillance testing for respiratory viruses as a condition of participation in health systems that serve these beneficiary populations. Any such reforms should be implemented through notice and comment rulemaking, to help assure coordination with public and private sector efforts to improve disease detection and response planning.

Concurrent to reimbursement reforms to support surveillance based on laboratory tests, financial support and broader stakeholder participation in low-cost surveillance efforts through other innovative monitoring methods can also lead to greater local awareness and responses to reduce disease spread. This includes financial support for ongoing wastewater surveillance for potential infectious disease threats, including efforts undertaken by health care organizations. The CDC's National Wastewater Surveillance System provides a foundation for more extensive and uniform local collection efforts. These local efforts may be coordinated by CDC and other Federal agencies so that electronic reporting is standardized across agencies, and results are accurate enough to provide greater perspective on disease spread.

Reforms to facilitate the use of testing for screening

Novel approaches to the utilization of testing products can support their enhanced use for screening purposes to reduce wide-spread transmission in high-risk patient populations. This is particularly important in periods of disease surge when stakeholders seek to most tactfully deploy medical products to mitigate transmission and infectiousness. Federal or state-level incentives to developers and health care providers can encourage the validated use of tests for screening purposes during disease surges. For example, regulatory guidance could provide support to validate use of pooled samples to reduce costs or extend limited supplies. Regulatory guidance can also clarify opportunities to utilize tests when faced with sparse resources, for example utilization of products past expiration dates.

Vaccines and Therapeutics

Like diagnostics, vaccines and therapeutics can have variable effects in supporting population health as well as individual treatment goals. Current products have shown transmission reduction capabilities that can be enhanced in new products that reduce both susceptibility to infection and level of infectiousness. More explicit consideration for population benefits in existing policy frameworks can encourage greater use of current and future vaccines and therapeutics to reduce population-level disease transmission. Past regulatory and coverage decision-making processes for both product types that have acknowledged benefits and risk beyond the individuals serve as building blocks for policy steps to enhance transmission reducing potential.

One relevant regulatory precedent related to benefits beyond a product user is the approval of vaccines for pregnant individuals to protect newborns. The pertussis and RSV vaccines have been approved to provide protection to newborns with no direct benefit to the pregnant person. The influenza vaccine is also recognized to provide benefits to both the pregnant individual and neonate. While not explicitly conferring a benefit through reduced transmission, these examples illustrate consideration of external benefits in determining a favorable benefit-risk assessment for a product.

Stakeholders can also build upon existing approval incentives and pathways to promote the development and use of therapies that provide significant population health benefits. These include priority review vouchers to incentivize development of products that address unmet medical threats in cases where direct financial incentives for development may be inadequate, and clarity about an accelerated approval pathway for population health product claims based on surrogate markers (e.g., symptom duration, impact on viral load).

Coverage, and thus access, for therapeutics and vaccines has also been shaped by some consideration of population-level benefits. When approaching coverage of vaccines, for example, ACIP has considered evidence on products beyond individual benefit and risk. ACIP criteria include intervention sustainability, impact on health equity, the urgency and magnitude of the problem, and benefits/harms, for both individual or population levels, based on evidence available. Based on these and other criteria, ACIP has expanded its recommendations for the use of the human papillomavirus and rubella vaccines, with explicit consideration for both individual and population-level benefit. USPSTF evaluation also incorporates criteria with a lens beyond individual benefit or risk. These include impacts on quality of life in evidence recommendations for pre-exposure prophylaxis for human immunodeficiency virus that referenced worry or anxiety about infection transmission, and ease of adherence that contributes to product uptake and thus potentially population as well as individual impact.

Reforms to support evidence generation mechanisms for population-level efficacy

A range of policy steps can facilitate further evidence development in the post-market space for vaccines and therapeutics to support uptake to realize population health benefits. As previously noted, both observational and interventional studies have been effectively utilized to understand the population-level benefits of vaccines. While advancing evidence generation is a priority for all medical technologies utilized as part of a population benefit framework, the focus here is on incentives for evidence development for vaccines and therapeutics.

Pragmatic, randomized trials can contribute evidence to better understand the transmission reduction efficacy of products with established strong individual benefits and remaining questions around population-level benefits. These pragmatic trials can be designed with simplified protocols to capture only the most relevant outcomes. During the COVID-19 pandemic, for example, the RECOVERY trial identified several effective treatments for inpatient use. The success of the RECOVERY trial raises the potential for a similar trial scoped specifically to transmission reduction outcomes with already approved therapeutics. However, developing necessary infrastructure for a pragmatic trial approach for transmission reduction and population health evidence may be more challenging than for demonstrating evidence of individual benefit. A platform trial approach that utilizes shared protocols and design for multiple viruses may make large, simplified trials for evaluation of population-level transmission reduction more cost-effective and efficient, but will still be challenging to operationalize.

More traditional clinical trials can also support regulatory label changes for medical products with an effect on transmission. Past post-market studies have supported label expansion for the pertussis vaccine. Pertussis vaccine indicated use expanded from active booster immunization in individuals 10 years and older to immunization during the third trimester of pregnancy. This expansion acknowledged that passive immunity during pregnancy would benefit newborns that were not yet immunized against Pertussis. In addition, a label expansion for the human papillomavirus vaccine to prevent certain types of cancer in boys and men recognized immunization in boys and men may contribute to a reduction in infection transmission to women and girls. However, there was not enough clinical evidence provided to support that claim, which highlights the need for improved evidence generation to support claims of transmission reduction as a population health benefit.

For the annual fall updates for some respiratory vaccines, FDA could provide a clearer pathway for post-market studies for label expansions related to transmission reduction. Requiring post-market studies would allow FDA to support timely approval of vaccines that are individually beneficial, while still encouraging vaccine sponsors to develop evidence on the potential broader population benefits of use of their products. The FDA and sponsors could also work together ahead of the fall respiratory virus season to align on expectations for these studies. Validated surrogate markers for transmission reduction could also make evidence development of population benefits easier. In addition, early alignment between product developers, standards coordinating bodies, and payers can better facilitate coverage and reimbursement for population-level use once proven.

Reforms to bolster access to products with population health benefits

In addition to building further evidence-generation infrastructure to support population-level use, additional procurement reforms that address coverage and reimbursement for products with population health benefits are necessary to facilitate access. Like diagnostics, continuing PHE-era flexibilities for use of medical products that demonstrate high transmission reduction benefits can facilitate access, particularly for populations who are hardly reached by the healthcare system. Enhanced reimbursement for the prescription of therapeutics by pharmacists can also support greater reliance on pharmacies as test-to-treat sites of care. When approaching reimbursement, value-based payment arrangements with manufacturers that produce further evidence on population-level benefits can facilitate coverage and utilization. These may be particularly important for novel therapeutics, which have less of a precedent of reducing transmission between individuals than traditional, injected vaccines. In order to support efforts by payers to promote uptake, health systems and professional societies can develop complementary education initiatives that promote voluntary, informed patient use of products.

In addition to novel reimbursement approaches, Federal and state stakeholders will play a key role in ensuring consistent access to product use, particularly in periods of disease surge. CMS can play a large role in facilitating

access in several ways. First, the Agency can build on existing performance measures in Center for Medicare and Medicaid Innovation (CMMI) models or CMS Accountable Care Organizations (ACOs) that capture uptake of vaccines and therapeutics to incentivize the use of products with demonstrated transmission reducing abilities. CMS can also play a large role in incentivizing the prescription and use of vaccines and therapeutics with payments that reflect the added value of transmission reducing products to both the individual and beneficiary population. On the Medicaid side, agencies may enter into procurement agreements to facilitate outcomes-based payment models that capture the population-level benefits of products and ensure that sufficient product supply is available in periods of disease surge. These procurement agreements may be supported by Federal bulk purchasing that provides additional safeguard to product supply.

Policy Implications: Encouraging "Next-Generation" Transmission-Reducing and Blocking Products

The financial commitment to the development of next-generation COVID-19 respiratory virus products under the Biden Administration provides a recent precedent for policy incentives to develop new products that are intentionally designed to better reduce or ultimately block transmission than current products. While our current regulatory and reimbursement policies provide a foundation for access and use of next-generation products, there are additional considerations for new products specifically designed to provide population-level benefits like transmission reduction. As described above, reforms to current mechanisms that can encourage label expansions and greater uptake of existing products, as well as new infrastructures to support such use, will help encourage the development, production, and adoption of products that can achieve greater transmission reduction benefits. In addition, reforms that encourage the premarket development and initial approval process for such products can build on incentives for more effective use of current products to realize a population-level strategy to contain and address infectious disease burden.

Continued development of next-generation vaccines and therapeutics can be incentivized by flexible employment of existing regulatory pathways. New product types, like immune modulators and host-directed therapeutics, can receive authorization or approval first with a surrogate marker representative of reducing disease transmission through an expedited review pathway. Following this initial regulatory review, a clear post-market regulatory path could describe how the marker could be validated to a clinical endpoint demonstrating transmission reduction, e.g., in high-risk population settings. Next-generation products can also demonstrate individual clinical benefits to first receive authorization or approval, while having a clearer pathway to obtain additional label indications (and associated benefits in terms of improved coverage, payment, and use) for demonstrated impacts on transmission reduction. Stakeholders can prioritize a population-level lens in pre-market clinical trial design, including the development and adoption of endpoints that assess transmission reduction, and selecting a study population/setting with a high likelihood of disease spread (though the product would need to be compared to the existing standard of care, which may require a large sample size and multiple settings to undertake cluster randomization to detect population benefits beyond individual use benefits). Updated versions of antiviral and monoclonal antibody products can also utilize take advantage of this flexible regulatory structure.

Implementation Considerations for a System-Wide Transmission Reduction Strategy

Achieving systematic population-level benefits through policy steps for increased, voluntary use of current and next-generation products requires translating this framework for infection reduction into public and private action, which requires administrative, cross-agency support at the Federal, state, and local levels. Stakeholders will require additional infrastructure and guidance to realize policy reforms. Key implementation considerations include supporting evidence generation to identify population-level benefits and obtain buy-in across stakeholders, enabling inter-agency coordination on policy steps to promote population-level benefit and voluntary uptake, and engaging health care organizations and the public in acting on the evidence and guidelines.

Aligned guidance to incorporate infection reduction considerations into policies that promote the development and availability of transmission reducing products

Based on current and emerging evidence on transmission reduction, agencies can align on guidance to better support the development and availability of transmission reducing products. Product manufacturing and delivery has to be scaled appropriately and sustainably to reach all parts of the health care system and other access points for patients. The use of products should also be monitored both to ensure consistent supply and to continuously assess effectiveness for transmission reduction. An interagency coordinating body led by the HHS operating division the Administration for Strategic Preparedness and Response and the newly formed White House Office of Pandemic Preparedness and Response Policy can facilitate these efforts, particularly as disease variants and areas of disease spread evolve.

Engaging health care organizations to promote population health and public engagement

Effective engagement of health care organizations will be critical to the success of implementing evidence-based guidance to reduce transmission and enhance demand for transmission-reducing products. Payment and other policy reforms that support health care delivery models will be needed to align with the transmission reduction framework. Academic medical centers provide a unique environment for transmission blocking research, clinician training, and clinical care that provides the opportunity to effectively deploy medical products to reduce transmission. Supported by technology and biomedical innovations, public and private health care reforms are increasingly prioritizing prevention, a shift to community-based care with early interventions, and building longitudinal patient engagement and trust to address population health challenges and rising health care costs. These health care reforms align with our framework of applying population level benefits to transmission reduction of respiratory viruses. For example, Medicare's growing accountable care organizations and accountable health plans, as well as community health centers with substantial Medicaid funding, are implementing steps to engage hard-to-reach patients in the community, using payment reforms linked to greater accountability for population health outcomes. These sites have also been crucial access points for test-to-treat models, with community health centers experienced higher rates of vaccination and testing.

Health care organizations can support public health leaders in communication and public engagement to achieve implementation of a successful transmission reduction strategy centered on population benefits. A comprehensive transmission reduction strategy requires awareness and greater use of evidence-based NPIs, increased uptake of currently available products, and development of next-generation technologies. A stakeholder value chain ties together the benefit derived from collaboration, along with specific roles and responsibilities at each stage of the product lifecycle. Further efforts are needed to clarify the value for each stakeholder to increase adoption of current products and to provide continued support for the development of next-generation technologies.

Conclusion

Adoption of a framework to incorporate population benefits into regulatory and reimbursement processes can position the U.S. as a leader in reducing transmission of respiratory viruses at the population level and advancing a more comprehensive infectious disease management strategy for the 21st century. Identifying actionable policy considerations within a larger framework can facilitate enhanced use of existing products and stimulate development of future products to better block and reduce transmission. A new vision, with a focus on containing the spread of infectious disease, leverages the current and future output of the biomedical research enterprise with the growing shift in value-based care to make a difference at a population level and protect individuals at the highest risk for severe outcomes. More work is needed on discerning the best mechanisms for evaluating the effectiveness of products, and other interventions, to inform implementation. The proposed regulatory, coverage, and payment policy steps present opportunities for Federal government agencies to work together with industry, academic, health system, and payer partners to lessen the fall respiratory viral disease burden.

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