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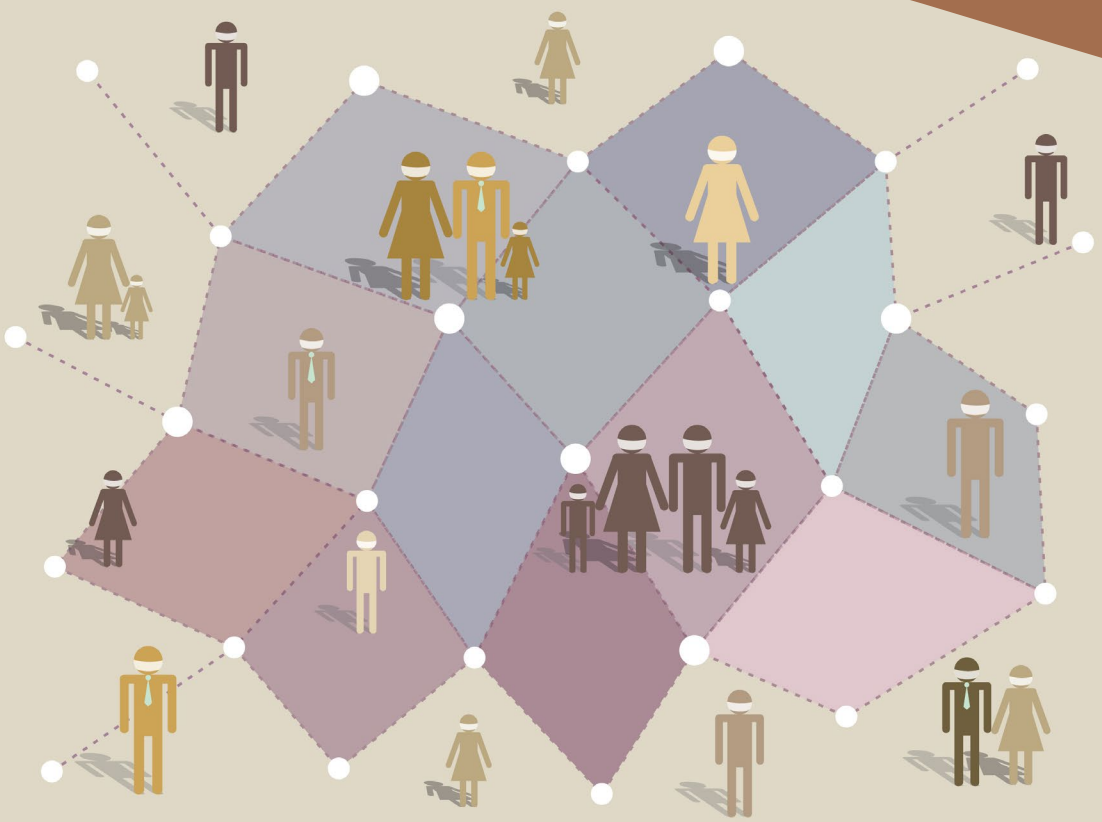
Supporting Evidence Generation of Indirect Benefits and Risks for Medical Products Used for Infectious Diseases



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INTRODUCTION

Unlike many other diseases, infectious diseases can negatively impact the health of the affected person as well as those around them, through transmission of the infection. Public health consequences from infection transmission have been particularly impactful for respiratory viruses such as respiratory syncytial virus (RSV), influenza, and SARS-CoV-2. Consequently, the development and evidence-based use of diagnostics, vaccines, and therapeutics for respiratory viruses have the potential for substantial health benefits not only for the individuals who use these medical products, but for others who can benefit through reducing transmission.[1] The "indirect" health benefits for others are important for assessing and communicating the overall value of these medical products.

While there is recognition of the importance of indirect health benefits, there is not yet a systematic approach to quantify, incentive, or integrate assessments of indirect benefits and risks for these products (please see *Integrating Health Benefits into Biomedical Policy: Key Reforms for Federal Agencies to Reduce Disease Transmission*). As a result, clear evidence on indirect benefits to inform decisions by individuals and their providers — as they assess benefits and risks to themselves and those in their immediate and broader communities — has not been a well-defined and consistent policy priority.

This paper is the second in a three-part series focused on understanding and increasing the indirect benefits of biomedical products. Here, we provide an overview of sources of evidence on indirect benefits, define the evidentiary needs for capturing indirect benefits, and provide a description of current and proposed approaches for evidence generation. We also highlight action steps for developing evidence on indirect benefits and propose policy recommendations for Federal agencies to generate and leverage evidence on the transmission reduction capacity and capability of vaccines, therapeutics and diagnostic products. Policy recommendations are summarized in **Table 1.**

Table 1 | Summary of Policy Recommendations

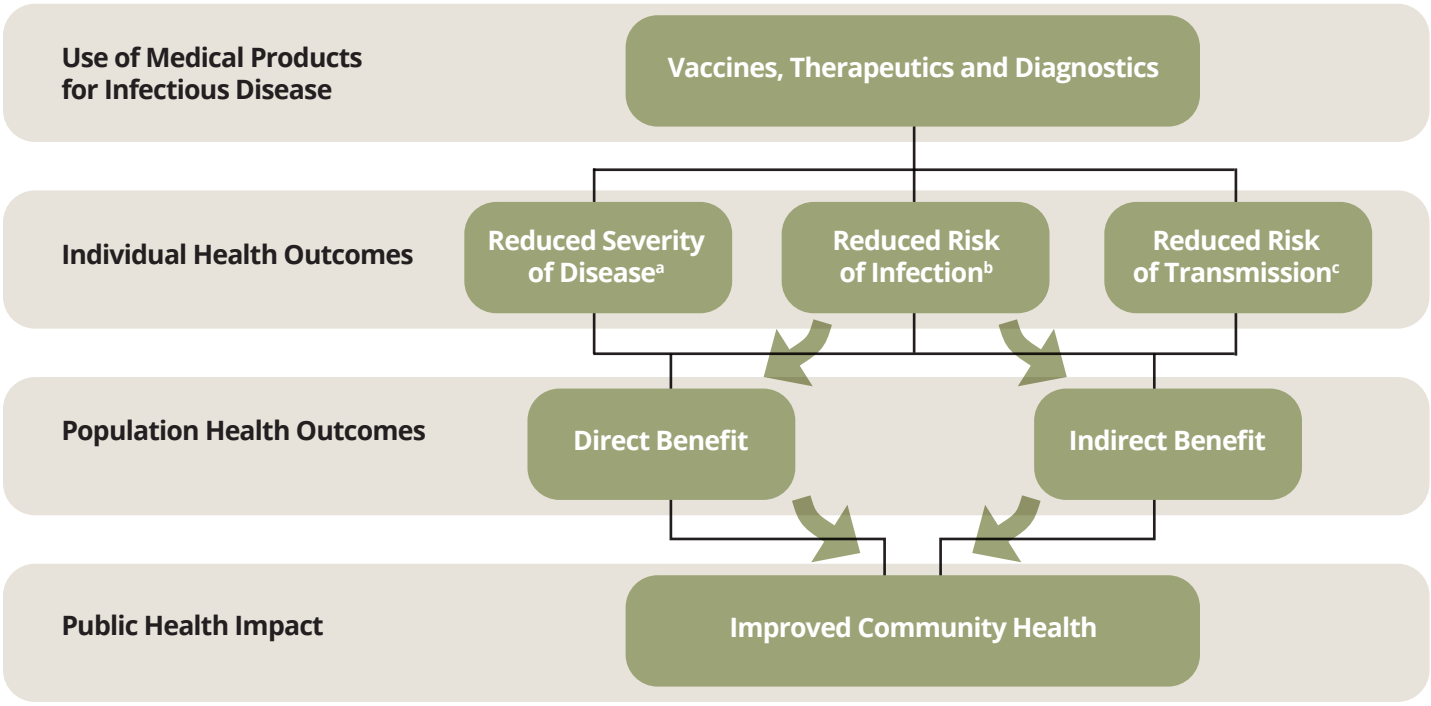
Category and Federal Agencies	Policy Recommendations
Supporting Indirect Benefits—FDA and NIH	• Release guidance on utilizing individual- and cluster-level randomized clinical trials that link individual endpoints with validated biomarkers for demonstrating transmission reduction, e.g. viral load - Clarify regulatory pathways to support comprehensive direct and indirect evidence development strategy for medical products - Collaborate on funding and study design • Congressional authorization of future user fee agreements or appropriations to: - Conduct research on best practices for study design - Identify platforms which support individual-and cluster-based randomization to generate evidence of indirect benefits for high-risk populations
Advancing Real-World Evidence Development on Indirect Benefits—FDA, CMS, VA, NIH, CDC, ASPR	• Develop smooth pathways into post-market population-based studies that refine suggestive evidence of indirect benefits from clinical trials - Support RWE best practices by developing guidance that addresses sufficient criteria for a label expansion on indirect benefits • Establish sustainable RWD and RWE infrastructure using within cohorts and populations to report data supporting transmission reduction claims • Identify funding opportunities to support quality improvement in health systems interested in optimizing product use to minimize population health impacts • Expand evaluations of test-to-treat and test-to-isolate programs—piloted by NIH, CDC and ASPR—to congregate settings, schools, shelters, and workplaces prioritizing use of cluster-randomized designs • Improve infectious diseases surveillance systems that may alert health care providers, public health officials, and the public to spur transmission reduction actions • Apply best practices from research on vaccines and other products with demonstrated indirect benefits to develop practical study designs, populations, and settings and validate measures and biomarkers for transmission reduction • Develop licensure criteria for diagnostics that consider public health and preventive use
Applying Research Findings to Regulatory Decisions and Communication—FDA, NIH	• Coordinate on best practices for communicating the indirect benefits of approved products - Acknowledge data collected and endpoints derived from individual and cluster-level randomized studies • Establish guidance on labeling of medical products that clearly lists out indirect benefits in plain language for patients and health care providers
Enhancing Reimbursement of Demonstrated Indirect Benefits—FDA, CMS	• Draft guidance for FDA to assist CMS in coverage decisions for indirect benefits • Incorporate quality improvement incentives to facilitate CMS paying for demonstrated claims of indirect benefits in addition to direct individual benefits for Medicare or Medicaid beneficiaries

The Importance of Indirect Benefits

The overall health impact of medical products that aim to reduce the burden of infectious disease, be it diagnostics, vaccines, or therapeutics, includes not just the direct impact of medical products on those who use them, but also indirect health benefits for others in the community through a reduction in transmission of the infectious agent.[1]

Figure 1 provides a conceptual summary of prior work that has sought to frame how to assess both direct and indirect benefits of medical products for community health impacts. Direct health benefits to those who receive vaccines and prophylactic therapeutics include a reduction in risk of infection when exposed to the infectious agent. Vaccines, therapeutics, and diagnostics (via their impact on individual actions) provide potential direct benefits to those who receive them by reducing the severity of disease — including death, hospitalization, and severity of symptoms. However, even among those with a relatively low individual risk of severe disease, use of these medical products may reduce transmission to others, including some who may be at a high risk of severe disease or death, thereby contributing substantively to the overall community health impact. For example, by choosing to use a product with substantial indirect benefits, an individual such as a worker who has significant exposures to others at work, or a person with higher-risk contacts at home, can contribute significantly to the reduction of disease transmission and community health burden.

Figure 1 | Conceptual Model for How Product Utilization Impacts Community Health Through Direct and Indirect Benefits



[a] Vaccines and therapeutics can decrease symptoms, risk of hospitalization and risk of death. Diagnostics can lead to early and appropriate treatment of other behavioral changes.

[b] Vaccines and prophylactic use of therapeutics can reduce individual risk of infection

[c] Vaccines and therapeutics can reduce the potential for transmission from an infected individual. Diagnostics can reduce transmission through individual behavioral changes or a more informed public health response.

Despite the potential importance of indirect benefits, quantifying the indirect benefits of medical products for infectious diseases is not incorporated systematically in regulatory, reimbursement, and other policies. Understandably, the traditional regulatory and reimbursement focus for a medical product has been on direct benefits to the individual; indeed, if a product has the potential for carrying any individual risk — as medical products generally do — ethical considerations will tend to preclude approvals based on indirect benefits alone. With most clinical trials for product approval thus focused on reliably estimating direct benefits (e.g., likelihood of a reduction in death or hospitalization) and individual risks as primary endpoints, additional data sources and analyses are likely needed to better assess indirect benefits. This might include secondary endpoints in individuals with potential indirect impacts (e.g., likelihood of being infected, duration and intensity of infectiousness), but such endpoints can increase the cost, duration, and complexity of clinical trials. Therefore, such evidence often comes later from observational data, including public health surveillance data or other real-world comparative studies. Ahead of such direct empirical evidence, evidence can also come from modeling studies of disease spread dynamics, incorporating parameters based on empirical evidence. For example, groups like the Vaccine Impact Modeling Consortium have worked to quantify the impact of vaccination and policy-related questions.[2]

These diverse current efforts provide a foundation for a more coordinated and comprehensive strategy for improving evidence generation on indirect benefits. Advances in data collection and analysis; development of new methodologies, standardization, and best practices for "non-traditional" study designs; and growing recognition by regulatory authorities of the potential value of evidence from studies other than randomized controlled trials provides unprecedented opportunities for stakeholders to generate evidence to improve individual and policy decisions about the use of medical products with potentially important indirect health impacts on the burden of infectious diseases. In particular, better coordinated and comprehensive evidence generation that captures indirect effects of medical products on infectious diseases could:

- Clarify a pathway to evidence-based, FDA-endorsed claims of indirect benefits for already approved products, and provide an evidence-based justification for reimbursement support by public and private payers (as discussed in Sussman, Canter, McClellan);
- Provide information to patients, and their health care providers and health systems, so that they can make more informed and confident decisions about product use based not only on their individual health but on the implications of their decisions for their families, contacts, and communities;
- Support more evidence-based policymaking by Federal health agencies with regard to the indirect benefits of medical products that can impact infectious diseases; and
- Clarify a pathway for product development programs to have a greater impact on the burden of infectious disease, including next-generation products that demonstrate better transmission reduction as well as individual health benefits.

Respiratory Viral Transmission: A Case Example

As we have noted, the notion of considering indirect benefits and risks in the overall management strategy of infectious diseases is not new. For respiratory viruses in particular, transmission reduction and its indirect health impact have been incorporated into some study designs and resulting regulatory approvals and policy initiatives to contain disease spread. In this section, we summarize such evidence for the role of indirect benefits in the use of vaccines, therapeutics, and diagnostics to date, as a starting place for further work.

Given the dynamic nature of transmissible infectious disease in a population over time, methods that bring together different sources of evidence, such as dynamic transmission modeling for interventions that had an impact on transmission of a pathogen, may be helpful.[3] Dynamic transmission models can provide insights into the total benefit and risks of vaccination programs and other interventions for infectious diseases through considerations of transmission impacts on

population health outcomes as well as economic impacts and other downstream effects.[4] Best practices for this approach provide guidance on the appropriate use of dynamic models to evaluate disease transmission and the management of uncertainty in dynamic models. Additional guidance overviews effective ways for reporting the results of dynamic modelling to transparently and credibly inform decision-making.[5]

For example, common respiratory virus vaccines are approved based on evidence of reduced risk of infection and particularly risk of serious disease in recipients. However, it has been long recognized that these vaccines may reduce viral transmission in a population. Defining transmission—along with developing and validating feasible measures for individuals and populations–is needed to guide future research that can determine how well existing and future vaccines impact transmissibility. **Appendix 1** provides examples of assessing transmission reduction using different study designs to contribute to the body of evidence for these indirect effects for not only vaccines but also therapeutics and diagnostics. It is important to note that typically these assessments of transmission reduction are done subsequent to the initial, individually randomized controlled trials assessing safety and efficacy for product approvals. Despite not being utilized for evidence generated to receive regulatory approval, cluster-based randomization has been employed to explore population-level health impacts of vaccines. Cluster-based randomization assigns groups of study participants to receive or not receive an intervention, or to receive different rates of intervention. From our review of the existing literature, further work is needed to implement product development programs that leverage the benefits of both individually and cluster-based randomization, while accounting for the challenges to reconcile the evidence generated from both types of study designs.

In particular, the development and approval of therapeutics for respiratory viruses provides insight into leveraging post-market evidence generation on indirect benefits. For example, antiviral therapeutics for the treatment of influenza were authorized for use in patients with influenza infections to reduce duration and severity of illness. Post-market assessments demonstrated their potential value for realizing indirect benefits—by reducing infection spread and severity within an at-risk community setting. This resulted in expanded indications for longer term prophylactic use post-exposure. This pathway of initial approval for direct benefits to an infected individual, followed by expansion to include further direct benefits of prophylactic use post-exposure, spotlights how uncertainty about indirect benefits often lingers after product approvals. Building off this example provides opportunities to design and build evidence to support claims of indirect benefits using approaches that combine traditional trial designs with modeling and real-world data.

Finally, diagnostic products play an important role in managing viral respiratory diseases, as well as other infectious diseases. However, these products currently provide even greater challenges in terms of evidence for their impact on transmission. Their impact depends on the infected person taking follow-on action (e.g., avoiding contacts, seeking treatment), which can help reduce transmission from the infected individual and protect those at risk of severe infection around them. With regular, widespread use and deployment targeted to higher risk settings, diagnostics can potentially have an important impact on infection transmission rates. Diagnostics can also be used for screening and can also enable more informed local community awareness and response with timely, secure, and reasonably complete sharing of individual results. Pooled testing—testing several samples together in one reaction—allows for greater efficiency to operationalize testing at a scale not possible with individual results. This could have larger public health benefits in assessing population-level infection rates, while accepting that the direct benefit to the individual may be lower than if they had tested individually. Some examples include pooled HIV testing of donated blood, and pooled COVID-19 testing of students.[6, 7]

These promising efforts to incorporate indirect benefits into evidence on population-health impacts are not yet aligned systematically and into a comprehensive framework. In the next few sections, we outline considerations for developing this evidence generation infrastructure—beginning with what kind of evidence could be collected and with what methodologies.

Defining Evidence that Captures Indirect Benefits

To build a more robust infrastructure for understanding and integrating indirect benefits of medical product use, stakeholders must first define what kind of evidence is most needed and feasible to obtain that will support individual and population health decision making.

Specifying Key Objectives for Evidence

To guide steps to improve the evaluation of potential indirect benefits of medical products, it is important to identify which potential policies may be informed by the additional evidence and the end goal for integration of this additional evidence into the identified polices. Put simply, the collected evidence—both the direct and indirect benefits and risk—should be framed around individual decisions and provider guidance related to administration of vaccines, therapeutics, and diagnostics.

Dynamic modeling is best suited to fully capture the indirect benefits of vaccination, namely herd immunity.[8] Notably, the amount of vaccination coverage—the extent of vaccine uptake as a percentage of the population—dramatically altered the results of the dynamic model as compared to a static model. Health technology assessments (HTAs), which are currently more common for primary prevention measures like vaccination and screening than for diagnostics and therapeutics can provide further opportunities to more fully integrate indirect effects, including indirect health effects for a community.[9] However, economic analyses of vaccine impact, which make up a portion of HTAs, often fail to fully incorporate societal health gains beyond the person receiving the vaccine.[10] Widespread use of dynamic modeling for health and non-health outcomes can shape holistically-derived policies.

In addition, the key objectives for the evidence generated on indirect benefits should be practically relevant to receiving versus not receiving a product, including for those individuals at low-risk of severe illness. Also important is to compare the distributional effects of alternative policies, that is, how the direct and indirect effects play out for different groups in the population. For instance, congregate living facilities, schools and families all comprise of individuals with varying levels of risk to severe disease. While newer approaches to incorporate tradeoffs between equity and efficiency are relatively new for health technologies and programs, there have been applications to vaccines that encompass indirect effects.[11] Grounding the evidence in a key objective allows for practical application of indirect benefits towards a feasible goal for improving the use of products. Understanding of the key objective by those individuals, who may only contribute to the community health impact by reducing disease transmission, is also important.

Identifying Outcomes of Importance

The next step in improving the evidence on indirect benefits is to clearly describe the information needed for decision-making. Building on our framework which defines indirect benefits, evidence of indirect benefits can be captured several ways: by measuring health outcomes such as number of new infections, duration of infectiousness, and measuring non-health outcomes that plausibly depend on infectious disease outcomes in the population studied, like number of school and work absences (including parental missed work for child illness). Quality of life can also be included for measurement, such as the economic and social outlook of children, exposed to prebirth vaccination.[12] Researchers may pull from a spectrum of data sources including clinical trials, occupational cohorts, electronic health records, wastewater testing, and other public health surveillance efforts. Most critically for health outcomes, it will be necessary to distinguish between those outcomes due to severe disease (e.g., hospitalization or death) versus outcomes due to transmission (e.g., number of infections).

In addition, to clinical endpoints such as a reduction in new infections, there are numerous potential surrogate endpoints that could be developed and validated for measuring transmissibility. Data to develop and validate these surrogate markers could be collected in studies that are focused on primary clinical outcomes of interest as either secondary or exploratory outcomes. This may include further development and validation of viral load or viral shedding measures, to better understand severity of disease and transmissibility or immunological markers such as antibody titers to better understand prevention of infection or reduction in disease severity.

Contextualizing Evidence for Decision-Making

Beyond identifying the key objective and most important health outcomes of evidence generated to assess indirect benefits, there are further factors for contextualizing the gathered information. Surrogate markers could be analyzed as secondary endpoints to enhance understanding the mechanisms of infection prevention and transmission reduction and subsequently enhance understanding of clinical outcomes in subgroups of patients or populations.[13] The information needed to analyze these secondary endpoints would be collected in tandem with direct measurements like subsequent infections. Another possibility to explore the extent of transmission reduction is through cluster randomization that positions indirect benefits as a primary outcome.

Understanding the generalizability of the results from the selected population is also needed to further contextualize generated evidence. The dynamic nature of indirect effects provides challenges for generalization. The number of individuals receiving the product, the disease prevalence among individuals in the population, the history of the product administration, the durability of the product, and the social mixing of product users and non-users all contribute to this dynamic nature and complicate the process of extrapolating effect sizes from a study population to another population. For example, studies in a population of high-risk individuals and/or in a high-risk setting would be more challenging to generalize to lower risk populations or low risk settings. An initial step towards addressing this complexity, can be to focus first on high-risk settings and then branch out into health systems or plans with existing longitudinal data collected on patients. Establishment of a study platform can pull data from electronic health records to explore how transmission reduction and infection prevention are affected by product use in a variety of health care settings.

Approaches to Evidence Generation for Indirect Benefits

Several study designs have been utilized and could be enhanced to collect desired evidence on indirect benefits. Selection of the most appropriate design depends on the specific evidence question(s) and the availability of data sources to address those question(s). In this section, we present a range of study designs and some key considerations for use in generating evidence for indirect benefits. While most of the existing evidence generation efforts have focused on vaccines, many of the considerations are applicable to therapeutics as well. Indeed, extending these study designs and considerations beyond vaccines is needed to support effective infectious disease management policies. While some individuals who are not at high-risk of serious illness or who otherwise do not feel comfortable taking a vaccine, they may be willing to consider indirect as well as direct effects from using a treatment or a diagnostic test. Understanding how use of these products may convey indirect benefits, e.g., transmission reduction, can foster informed individual- level decision-making by health care practitioners and Federal agencies seeking to balance community benefits as one input into a broader dimensional analysis for policymaking.

Interventional Studies in Controlled and Real-World Settings

The gold standard for assessment of the safety and efficacy of medical products has been double-blind randomized controlled trials, with the goal of using the evidence generated for meeting requirements for regulatory approval. Randomized controlled trials have been largely used to explore vaccine efficacy with a focus on protection of individuals from contracting symptomatic and/or severe disease. Studies are typically designed to measure this direct effect among those who receive the vaccine in comparison to those who do not (control group). Most recently, for COVID-19 vaccines, infection prevention and seropositivity were secondary endpoints considered in the assessment of vaccine efficacy while symptomatic infections were considered primary endpoints. This expansion of endpoints of interest illustrates how endpoints that may be important for both individuals and the community can be included in individual-level randomized trials. It also demonstrates that trials measuring direct effects could be extended to estimate both direct measures and surrogate markers of indirect effects, which could be linked more explicitly

to modeling for synthesizing such evidence into analyses of likely indirect health impacts. However, validation studies in appropriate populations and settings would be required for new measures and surrogate outcomes before relying on them in modeling studies. Even rigorous and valuable individual-level clinical trials are likely to benefit from complementary real-world evidence studies that more directly assess indirect benefits on contacts of those who receive treatment.

For vaccines, there is a notable history of pragmatic studies designed to assess population-level effects of vaccination beyond those on the vaccinated person. Cluster-based randomization can more directly estimate transmission reduction and resulting indirect health effects of greater use of a medical product within a defined population. For example, large-scale cluster randomization designs can evaluate the overall effectiveness of a vaccine in the study population with statistical analysis dedicated to individual- and cluster-level variables. A cluster-randomized effectiveness trial of typhoid vaccination in India measured the protective effectiveness of the vaccine in those who were vaccinated, as well as the indirect protection to unvaccinated residents living around vaccinated clusters.[4] In addition, there may be opportunities to evaluate serological endpoints.

Cluster-randomized interventional studies have also explored real-world evidence on population health with the introduction of widespread, accessible diagnostic testing. For example, the large-scale distribution of tests in specific Michigan municipalities resulted in decreased average case rates for COVID-19.[14] This intervention was analyzed during the Delta variant-driven surge in infections demonstrating the value of real-world studies, especially with increasing use of real-world data for utilizing information already collected as part of electronic health records.

Retrospective and Prospective Observational Studies

Encompassing a broader range of "real-world" evaluation methods, well-designed observational studies are useful and increasingly feasible to understand effectiveness and safety of medical products in varying environments, specific populations, and with consideration for other elements that may impact generalizability and reproducibility. In particular, observational studies have been long employed to evaluate the effectiveness of vaccination campaigns. Surveillance of influenza in communities in Michigan demonstrated that a vaccination program of schoolchildren in one community resulted in a lower rate of respiratory illness as compared to a neighboring community without the vaccination program.[15] The impact of vaccination campaigns in Scandinavian countries on the incidence of meningitis caused by *Haemophilus influenzae* b was observed over a 15-plus year period, providing insights far beyond what individual-level clinical trials are capable of on both direct and indirect effects.[16]

The COVID-19 pandemic produced a remarkable expansion in the number and kinds of observational studies of indirect vaccine effects. Observational assessments of virus transmission within households and communities provided evidence relevant to understanding how products may disrupt transmission. For example, observational studies highlighted the ability of parental vaccination to protect unvaccinated children within Israeli households.[17, 18] Protection of the children was assessed using the difference in risk of infection for susceptible children with vaccination of one versus two parents. The prevention of household transmission was also assessed by exploring the risk of a vaccinated, infected parent to infect an unvaccinated child. Such observational methodologies to assess the impact of medical products on household transmission of COVID-19 have also been used to assess how medical products may affect transmission of other pathogens and in other settings, such as workplaces and congregate living settings.[19, 20, 21]

Mathematical Modeling Studies

Modeling provides opportunities to extrapolate estimates of reduced susceptibility and/or infectiousness of vaccinated or treated individuals to understand the magnitude of effects at the population level under varying transmission conditions and levels of uptake. Models can both inform the design of interventional or observational studies and be informed by results of those studies.[22] In the simplest case, a model can assess how use of a vaccine, treatment, or diagnostic with a particular documented effect on reducing transmission (to and/or from vaccinated individuals, or from treated or diagnosed individuals) will affect overall incidence of infection over time in a population where it is used at a certain coverage level.

For example, new technologies and data types offer

the opportunity to enhance modeling studies of the transmission effects of vaccines. A theoretical study has shown how use of deep genomic sequencies along with contact tracing data can produce estimates of who infects whom that can in turn produce estimates of transmission effects even with only individual level data.[23] The value of such approaches was shown in a modeling study in COVID-19 where contact tracing data in the UK led to estimates of the infectiousness of vaccinated, traced cases relative to unvaccinated ones. Future directions include enhancing such studies with sequence data as well.[24]

As we have described above, such dynamic models can be most informative if reliable estimates of the key direct and indirect effects of a medical product are available. When these outcomes have not been empirically assessed, as is often the case for indirect effects, a model can use impacts on surrogate metrics such as pathogen load or duration of shedding, to extrapolate potential effects of a vaccine, treatment, or diagnostic on surrogates of transmission reduction.[25] The use of mathematical and conceptual or theoretical frameworks allows for consideration of how medical products impact not only individual trajectories but population health.[26]

While direct effects to individuals can also be determined, opportunities for assessing indirect effects in a population can be where these modeling studies are most valuable when assessing interventions for infectious disease. For example, transmission may be dependent upon the interaction of viral load (when viral load has been established to be correlated with infectiousness) and duration of time with that established viral load. Importantly, this kind of modeling can highlight the importance of operational aspects that are not measured or not central to clinical trials, such as the speed of results from a diagnostic, which can be major determinants of their population-level effects (since transmission effects of a diagnostic begin only when the result is known).[27]

Actionable Steps for Improving Evidence on Indirect Benefits

We have identified some key practical considerations for improving evidence on key mechanisms for transmission reduction. We have also illustrated these considerations using products that have potentially important implications for reducing the population impact of respiratory viruses. Next, we provide actionable steps to advance more standard, routine evidence generation on indirect health effects of medical products intended to address infectious disease threats.

The first step is to employ a clear, dynamic model to evaluate whether a product is likely to have important indirect health benefits. The next priority will be to identify the key primary objectives and relevant outcome measures, as well as the key secondary objectives and surrogate outcome measures, and how they could be collected. Primary objectives and relevant outcomes will initially encompass direct effects with individually randomized studies. Complementary exploration of secondary objectives and surrogate outcomes can be implemented within the same study. As the most important populations and settings to investigate are further revealed, cluster-based randomized studies can draw out the broader indirect effects tied to product utilization. To further contextualize the evidence needed for generation, RWD sources — including electronic health records and more rapid, accurate testing measures can be deployed. To ensure that dynamic models are continuously improved, a plan is needed to refine parameters based on the results of interventional and observational studies.

Depending on the product, evidence on indirect impacts may be needed for prevention versus pre- or post-exposure use. For common respiratory viruses, vaccines are preventive interventions to reduce risk and severity of infection. Antiviral or monoclonal antibody therapeutics, however, are often used in infected individuals to reduce duration and severity of disease — which could also lead to significant indirect impacts if infectiousness is significantly reduced — but they may also be used in uninfected individuals pre- or post-exposure to reduce risk and severity of infection. Pre-exposure use of therapeutics can fill a critical unmet medical need for immunocompromised individuals, who do not demonstrate a strong immune response following vaccination. All three uses have been studied for individual-level benefits, however antiviral therapeutics may also help to reduce disease transmission leading to community-level benefits. Such applications should seek to identify empirically-measurable

populations where such assessments could be conducted – likely including impacts of individual use on higher-risk populations but potentially including a range of risk levels or settings.

Similarly, diagnostic tests have indirect benefits both in screening versus individual diagnosis benefits and risks, as well as indirect benefits and risks. The ability of diagnostic tests to accurately identify infected individuals early in their infection is likely critical for their effectiveness in reducing transmission. Differences in sensitivity and specificity of diagnostic test products and the impact of sample type and ease of sample collection are important considerations. For transmission reduction, individual-level analysis of test results can be complemented by focused dynamic modeling. The timeliness of results and frequency of testing are typically more important to transmission reduction than sensitivity, indicating that the best test for clinical purposes (highly sensitive) might not be the best for transmission reduction.[28] Testing in individuals without symptoms versus those with symptoms is also an important consideration. To accomplish this objective, tests can be made more available in workplace settings, educational institutes, communities and for individuals to use in their household.

Some forms of screening tests, including pooled testing, may have little or no direct benefit to individuals (for example if the pooled test does not lead to identification of which individual is infected) but may be useful in identifying outbreaks faster and more precisely, with benefits for populations. Pooled tests possess lower sensitivity but with a clearer path for indicated use, can foster follow-on interventions, including voluntary use of medical products and behavioral changes. Techniques for pooled saliva and wastewater specimen surveillance for respiratory virus detection also vastly improved during the COVID-19 pandemic. There may be a role for these types of surveillance systems to detect outbreaks, alert health care providers, public health officials, and the public so that appropriate action can be taken to reduce infection transmission.

As we have noted, these strategies are relevant to a range of respiratory viruses, but also to advancing evidence on the indirect benefits of medical products for other infectious diseases. The test-to-treat approach pairs a diagnostic test with rapid access to treatments. A cluster-randomized pragmatic trial design was used to evaluate the impact of universal testing and treatment on individual outcomes and incidence rates of HIV infection in Zambia, South Africa, and Botswana.[29, 30] Similarly, a Test-to-isolate approach can pair regular, asymptomatic testing to screen for individuals who are infected in environments prone to disease transmission and/or inhabited by individuals at high-risk of severe disease, such as congregate care facilities with measures to contain outbreaks.

Policy Recommendations to Support Better Evidence for Indirect Benefits

The following policy reform could leverage the feasible strategies for improving evidence on indirect effects of medical products for infectious diseases.

Research funding agencies and regulatory agencies should develop clearer pathways to support a comprehensive direct and indirect premarket evidence development strategy for medical products that may plausibly have significant indirect benefits. These pathways should be supported by more comprehensive research funding strategies and regulatory guidance for developing claims. While the need for demonstrating individual benefits for an infectious disease product that addresses significant unmet needs is an urgent priority, such individually randomized clinical trials can potentially be designed to develop suggestive evidence on indirect benefits and could be paired with a smooth pathway into timely postmarket population-based studies to refine such evidence. This may include a strategy for developing and validating measures and biomarkers for transmission reduction such as viral load, a combination of cluster and individual-level randomized trials to assess indirect benefits along with direct benefits where feasible, and potential "platform" opportunities and best practices for study design in real-world, postmarket settings. Such platforms or model applications should prioritize high-risk populations for evaluating the indirect benefits of vaccination. Target groups may be selected as was done in Finland for avian influenza vaccination.[31] Evaluations can be designed by combining a trial with cluster-level randomization

of health care facilities measuring surrounding community levels of disease incidence with individual-level assessments of viral load. Congressional authorization of future user fee agreements or appropriations can also facilitate the conduct of research on best practices for study design and platforms, which support individual-and cluster-based randomization to generate evidence of indirect benefits for high-risk populations.

Beyond premarket evidence generation; research funding, regulatory, public health, and health care agencies can collaborate on **the development of sustainable real-world data and evidence infrastructure within cohorts and populations to support transmission reducing claims is also needed.** Additional clarification of pathways, best practices, and sufficient criteria for real world studies can drive further development and use of real-world evidence, specifically for label expansion to demonstrate claims of transmission reduction. Vaccines are one promising use case given the existing body of evidence and prior work. Integral to this effort will be leveraging health economics methodology and outcomes to build methods and outcomes of infectious disease transmission to assess indirect benefits. Systems can also incentivize collecting data with appropriate study designs to align with ongoing quality improvement activities occurring within health care systems to minimize the population impact. In addition, opportunities for vaccine studies in workplace settings where employers, employees, and health plans have a common goal to keep the workforce healthy and precedent for workplace vaccination clinics should be assessed. Evaluations of test-to-treat and test-to-isolate programs can also be expanded, building off programs piloted for COVID-19. Improved infectious diseases surveillance systems may alert health care providers, public health officials, and the public to spur transmission reduction actions. Enhanced surveillance systems can also aide in the refinement of dynamic models to complement infrastructure for real-world data and evidence generation.

For all types of products, **taking best practices from research on vaccines and other products with potentially important indirect benefits to improve evidence (particularly real-world evidence)**. This includes considerations for practical study designs, populations, and settings such as cluster-randomized trials to assess infection rates in untreated but exposed individuals as well as studies in households and congregate settings. For instance, a cluster-level randomization of households can be used to evaluate the impact of treating infected individuals rapidly with antiviral drugs or monoclonal antibodies on the incidence of disease in the household, like previously done in influenza studies.[32] This study could be partnered with an individual-level observational study of changes in viral load to the infected individuals within households.

With regard to diagnostics, **development of licensure criteria for diagnostics that considers public health and preventive use is needed.** In addition, expanded evaluations of test-to-treat and test-to-isolate programs in congregate settings, schools, shelters, and workplaces to better understand their role in potentially reducing transmissions is needed. Both cluster-randomized and observational studies can be utilized to evaluate community-wide transmission of disease with the use of screening tests in high-risk settings, like hospitals. Such criteria should consider the possibility that diagnostics may be better for transmission reduction while being worse for clinical diagnosis, and develop appropriate criteria for each.[33]

Taken together, these efforts can contribute towards a robust, sustainable evidence generation infrastructure to capture the indirect benefits of vaccines, therapeutics, and diagnostics across the product lifecycle. Subsequently, it will be critical for **research funding and regulatory agencies to coordinate on best practices for communicating the indirect benefits of approved products.** Communication relaying the indirect benefits of products would acknowledge data collected and endpoints derived from individual - and cluster-level randomized studies, along with real-world settings. Guidance on the labeling of medical products that clearly lists out indirect benefits in plain language for patients and health care providers would also need to be formulated.

Evidence generation processes and infrastructure for indirect benefits will also need to enhance reimbursement policies for these products. Draft guidance from regulatory agencies can assist payers in coverage decisions for indirect benefits. Furthermore, health care systems and providers can use quality improvement incentives to facilitate payment for demonstrated claims of indirect benefits in addition to direct individual benefits for beneficiaries.

CONCLUSION: ACCELERATING PROGRESS

Advanced evidence generation on indirect benefits can better align use of biomedical products to community health impact through outcomes like transmission reduction. Defining the evidence to be generated is needed to consider decision-making that will be informed downstream. Along with evidence definition, understanding the advantages of different approaches can facilitate comprehensive evaluation of the indirect benefits for vaccines, therapeutics, and diagnostics. Further practical considerations are needed to specifically apply the generation of evidence on indirect benefits to respiratory viruses. To encourage better evidence generation on indirect benefits, policy changes can create sustainable systems that leverage mathematical models to inform randomized controlled trials, pragmatic trials, and observational studies. Better evidence generation on indirect benefits can distinguish individual- and community-level benefits for products to allow for informed decision-making by individuals on voluntary use of products.

Appendix 1 | Evidence Generation Sources for Assessing Population-Level Impacts of Vaccines, Therapeutics, and Diagnostics

Modality	Endpoint	Reference
Cluster Randomized Controlled Trial	Indirect effects, infection and/or mortality	https://pubmed.ncbi.nlm.nih.gov/1899778/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9300768/ https://pubmed.ncbi.nlm.nih.gov/22028630/ https://pubmed.ncbi.nlm.nih.gov/19950412/ https://pubmed.ncbi.nlm.nih.gov/30711064/
	Indirect effects, therapeutics	https://pubmed.ncbi.nlm.nih.gov/30711064/ https://pubmed.ncbi.nlm.nih.gov/34508582/
	Indirect effects, diagnostics	https://pubmed.ncbi.nlm.nih.gov/34534517/
	Serological evidence of incidence	https://pubmed.ncbi.nlm.nih.gov/36962857/
Prophylaxis Randomized Controlled Trial	Infection in contacts of disease-positive index cases	https://pubmed.ncbi.nlm.nih.gov/11176912/ https://pubmed.ncbi.nlm.nih.gov/20121573/ https://pubmed.ncbi.nlm.nih.gov/14745701/ https://pubmed.ncbi.nlm.nih.gov/12447733/
	Frequency of viral shedding	https://pubmed.ncbi.nlm.nih.gov/20121573/
Test-and-Treat and Test-to-Isolate Randomized Controlled Trial	Incidence of infection in intervention vs control periods	https://pubmed.ncbi.nlm.nih.gov/36610058/
	Incidence of infection in population cohorts	https://pubmed.ncbi.nlm.nih.gov/24524229/, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6587177/
	Incidence of hospital admissions	https://pubmed.ncbi.nlm.nih.gov/37963697/
Observational Study	Household member incidence	https://pubmed.ncbi.nlm.nih.gov/35084938/
	Infectiousness estimated via contact tracing or proximity	https://pubmed.ncbi.nlm.nih.gov/34986294/ https://pubmed.ncbi.nlm.nih.gov/36593393/
	Infectiousness estimated via contact tracing or proximity	https://pubmed.ncbi.nlm.nih.gov/9841843/ https://pubmed.ncbi.nlm.nih.gov/38093182/
	Workplace spillover effects, discordance between testing methods	https://www.medrxiv.org/content/10.1101/2022.01.04.22268770v1
	Vaccination rate in school children, antibody response to vaccination, infection in vaccinated and non-vaccinated age group	https://pubmed.ncbi.nlm.nih.gov/5433709/
	Vaccination rate in school children, antibody response to vaccination, infection in vaccinated and non-vaccinated age group	https://pubmed.ncbi.nlm.nih.gov/33901423/ https://pubmed.ncbi.nlm.nih.gov/34250518/
	Average cases during intervention and post-intervention	https://pubmed.ncbi.nlm.nih.gov/35411342/
Mathematical Models	Incidence in unvaccinated (indirect effect)	https://pubmed.ncbi.nlm.nih.gov/1899778/ https://pubmed.ncbi.nlm.nih.gov/37152676/ https://pubmed.ncbi.nlm.nih.gov/31402591/
	Transmission using contact tracing, genomics	https://pubmed.ncbi.nlm.nih.gov/34039898/
	Viral load/infectiousness	https://pubmed.ncbi.nlm.nih.gov/34469363
	Prevented inpatient hospitalizations, ER visits, and primary care visits	https://pubmed.ncbi.nlm.nih.gov/35968866/ https://pubmed.ncbi.nlm.nih.gov/32248817/
	Time to infection	https://pubmed.ncbi.nlm.nih.gov/38348581/
	Vaccine durability and eligibility targeting	https://pubmed.ncbi.nlm.nih.gov/30890385/
	Infections, life expectancy, lifetime-related disease costs, cost effectiveness ratios	https://pubmed.ncbi.nlm.nih.gov/37986879/ https://pubmed.ncbi.nlm.nih.gov/31025025/ https://digital.lib.washington.edu/researchworks/items/ec099017-e950-40fd-b6df-3feca5cc36ce

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