Innovations in Prevention: Implications for Pediatric Patient Access and Public Health

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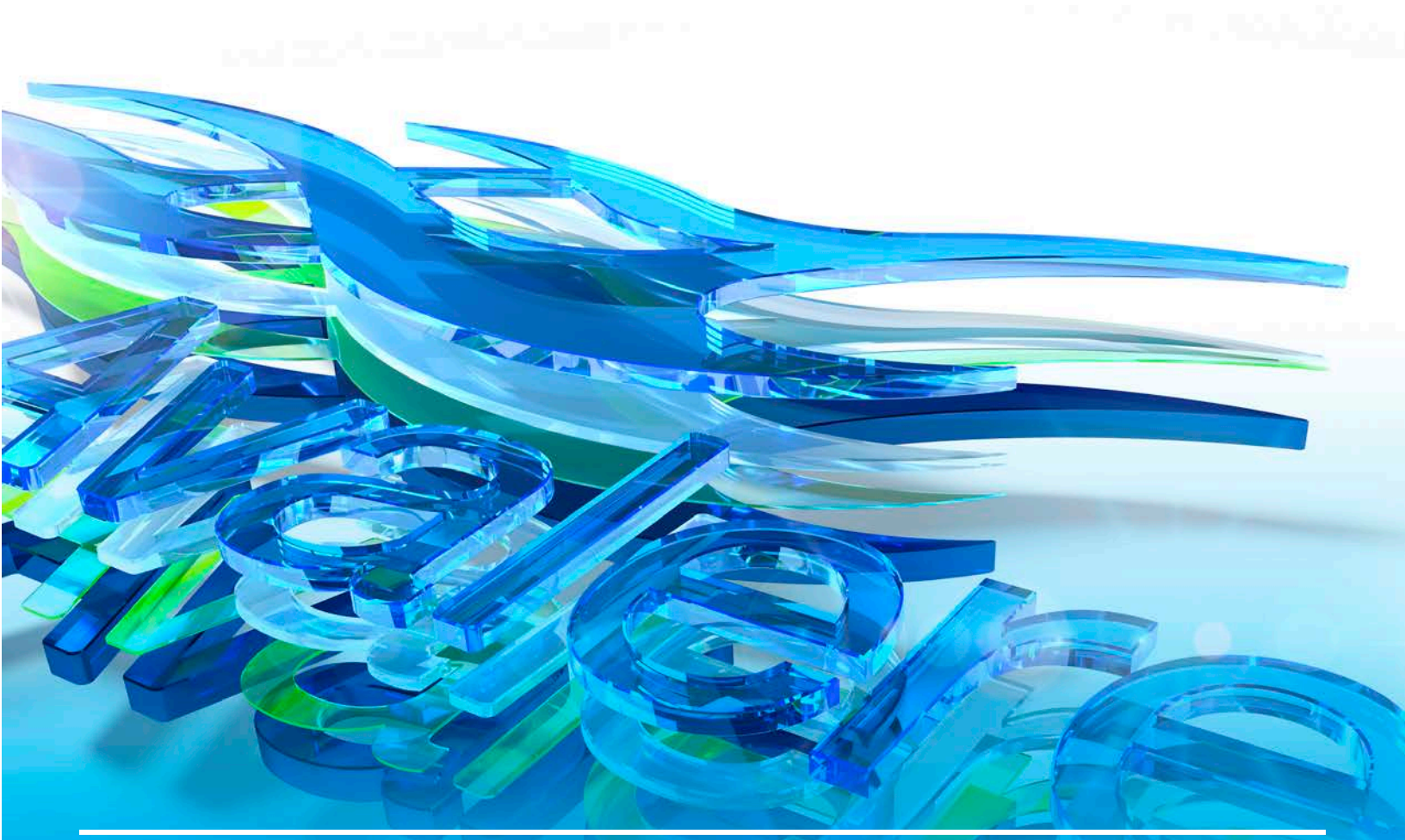

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Introduction

Over the last decade, the US pipeline of preventive products has expanded as new, innovative technologies move through later stages of clinical development. As the pipeline of novel vaccines expands, so does the pipeline for other "vaccine-like" products. Sharing similar characteristics to vaccines, vaccine-like products are intended to, or may be indicated for, the prevention of infectious disease, especially for diseases for which no vaccine is currently available. In particular, they may impact public health among pediatric populations through passive immunization through the direct administration or transfer of antibodies to the body. However, they remain in a "grey zone" between traditional drugs and vaccines, impacting their coverage and access under current US insurance requirements and public health programs. The nature of these products results in ambiguity as to their inclusion in traditional vaccine access pathways. Current vaccine-like products, including monoclonal antibodies (mAb) and immunoglobulins (Ig) administered prophylactically and which are indicated for narrow populations, have not historically been included in traditional vaccine access pathways, such as the Vaccines for Children Program. The addition of vaccine-like products to such programs may have implications for uptake and public health, especially among pediatric populations.

While the US recognizes the public health value of vaccines and has invested in developing insurance and access pathways to facilitate their uptake in the pediatric population, these pathways are not clearly available for vaccine-like products. Current access pathways for traditional drugs may present several barriers to patient access, which can ultimately impact patient uptake, result in health disparities, and impede public health goals. There is uncertainty regarding whether the coverage and access pathways established for vaccines will be applied to these preventive products.

Given the public health implications of higher access levels for preventive products, it is important to consider how access pathways differ between traditional drugs and vaccines and whether vaccine coverage and access pathways may be applied to vaccine-like products. Stakeholders should evaluate distinct access considerations for vaccine-like products under each pathway.

The VFC Program Serves as a Model for Childhood Vaccine Access and Uptake

Driven by a US measles resurgence, the Vaccines for Children (VFC) Act was enacted in 1993 to provide no-cost vaccines to children and ensure that eligible children do not miss necessary vaccines due to the inability to pay.[1] The VFC program's nationwide infrastructure ensures

[1] Centers for Disease Control and Prevention. Walker, Allison et al., "Reduction of Racial/Ethnic Disparities in Vaccination Coverage, 1995-2011." *MMWR* 63, no. 1 (April 2014): 7-12. Available here.

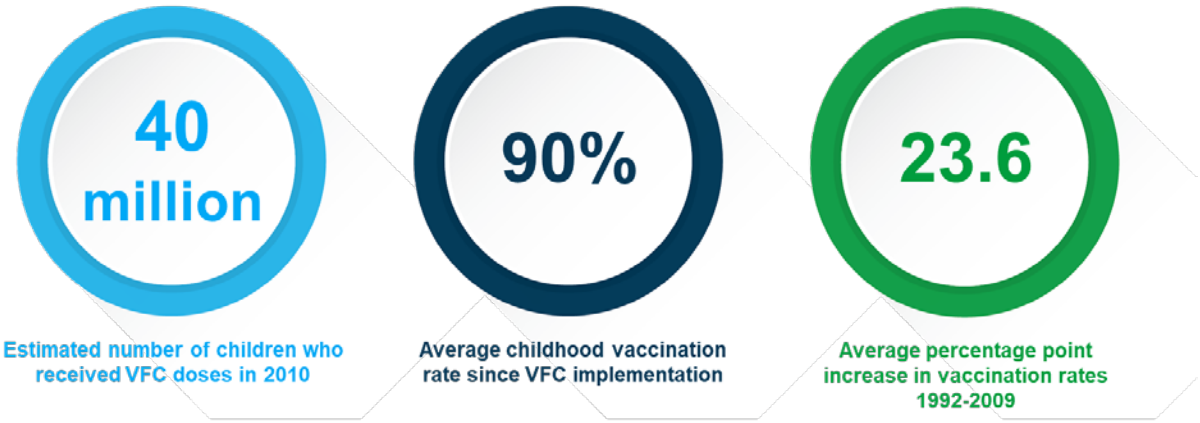
broad vaccine access and has been instrumental in increasing pediatric vaccine uptake for all children in the US over the last quarter century.

Prior to VFC's implementation in 1994, measles outbreaks disproportionately impacted high-density, low-income, inner-city populations and were fueled by inadequate measles, mumps and rubella (MMR) vaccination among uninsured children.[2] Significantly lower vaccine uptake was observed in children living below the federal poverty level, indicating a correlation between socioeconomic status and vaccine uptake.[3] According to a 1993 analysis of vaccine uptake, untimely and missed vaccinations were observed in children who were either referred by a primary care physician to other settings of care or who were unable to pay the associated out-of-pocket costs (OOP).[4] As a result of vaccine uptake discrepancies between 1989-1991, children in racial and ethnic minority populations were at a 3-16 times greater risk for measles than White children.[5]

Notably, racial and ethnic disparities in vaccine uptake narrowed following VFC implementation.[6] Prior to the VFC program, vaccination rates were higher among White children, with nearly a 5 percentage-point difference in diphtheria, tetanus, and pertussis (DTaP) vaccine uptake between White and Black children, and an almost 9 percentage-point difference between White and Hispanic children prior to VFC.[7] Following VFC implementation, which increased access to vaccines without cost-sharing, annual estimates of both MMR and polio vaccination coverage increased among all children aged 19-35 months.[8] Vaccine uptake rates between low-income and minority populations converged by 2010.[9] The VFC program became the foundation for pediatric immunization for underinsured and uninsured children, having been uniquely designed to ensure unencumbered access to vaccines for individual and population-level benefit.

[2] Centers for Disease Control and Prevention. Whitney, Cynthia et al., "Benefits from Immunization During the Vaccines for Children Program Era – United States, 1994-2013." *MMWR* 63, no. 16 (April 2014): 325-355. Available here.
[3] Centers for Disease Control and Prevention. "Vaccination Coverage by Race/Ethnicity and Poverty Level Among Children Aged 19-35 Months – United States, 1997." *MMWR* 47, no. 44 (November 1998): 956-959. Available here.
[4] Centers for Disease Control and Prevention. "Physician Vaccination Referral Practices and Vaccines for Children – New York, 1994." *MMWR* 44, no. 1 (January 1995): 3-6. Available here.
[5] Centers for Disease Control and Prevention. Walker, Allison et al., "Reduction of Racial/Ethnic Disparities in Vaccination Coverage, 1995-2011." *MMWR* 63, no. 1 (April 2014): 7-12. Available here.
[6] Centers for Disease Control and Prevention. "Physician Vaccination Referral Practices and Vaccines for Children – New York, 1994." *MMWR* 44, no. 1 (January 1995): 3-6. Available here.
[7] Walsh, Brendan, Edel Doherty, and Ciaran O'Neill "Since the Start of The Vaccines for Children Program, Uptake Has Increased, And Most Disparities Have Decreased" Health Affairs 35, no. 2 (February 2016). Available here.
[8] Centers for Disease Control and Prevention. Walker, Allison et al., "Reduction of Racial/Ethnic Disparities in Vaccination Coverage, 1995-2011." *MMWR* 63, no. 1 (April 2014): 7-12. Available here.
[9] Walsh, Brendan, Edel Doherty, and Ciaran O'Neill "Since the Start of The Vaccines for Children Program, Uptake Has Increased, And Most Disparities Have Decreased" Health Affairs 35, no. 2 (February 2016). Available here.

Figure 1 – The Vaccines for Children Program Provides Vaccines to Millions of Children



Currently, the Advisory Committee on Immunization Practices (ACIP) votes to determine which products are included in VFC. However, it remains unclear whether novel products are within the scope of the VFC and whether ACIP would evaluate a novel vaccine-like product.

In the absence of an ACIP recommendation, which could grant a vaccine-like product coverage without cost sharing in the commercial and Medicaid expansion markets and potential inclusion in the VFC program, a vaccine-like product is likely to be covered as a traditional drug.

Expansion of the VFC program to include vaccine-like products indicated for infants and children may ensure these populations do not forego preventive care due to cost. Without an ACIP recommendation, and ability to be included in the VFC program, vaccine-like products are likely to be covered as traditional drugs. Further, the term “vaccine” has not been defined in the VFC statute and as will be discussed, without an ACIP recommendation, patients may be further exposed to variable product coverage across plans and could have OOP costs.

The Expanding Pipeline of Vaccine-Like Products May Necessitate a Review of Existing Access Pathways

The biopharmaceutical pipeline includes several vaccine-like products, including mAbs and other biologics and small molecule drugs. While these products prevent infectious disease much as vaccines do, important definitions which govern US vaccine coverage and access pathways and programs, beyond VFC, do not account for their existence, nor do they account for the role they could play in protecting and improving public health. Just as the term “vaccine” has not been defined in the VFC statute, a term which defines vaccine-like products has also not been established. Thus, existing vaccine frameworks are not clearly inclusive of vaccine-like products, which have yet to be appropriately characterized in current US policy.

Vaccine-like immunoglobulins indicated for infants and children, including for hepatitis B and rabies, have historically been recommended for use in conjunction with vaccines. However, emerging vaccine-like products may be indicated for broader use in the infant and child population to prevent diseases for which vaccines do not yet exist, including respiratory syncytial virus (RSV) and human immunodeficiency virus (HIV). Unlike many currently marketed immunoglobulins (Igs), such as those for hepatitis B and rabies, which are administered following potential disease exposure, many vaccine-like products may be indicated and recommended for prophylactic use identically to vaccines.

Though these products closely resemble vaccines in that they may reduce the incidence of infectious disease in broad populations, such products prevent infection through passive, rather than through active immunization. Current vaccine coverage policies, however, only fully contemplate coverage for and access to vaccines that prevent infection through active immunization. If mAb or Ig, differing only by its mechanism of action, provided the same clinical benefit as a recommended vaccine, it would likely not be included in the current vaccine framework.

Figure 2 –Stakeholders May Benefit from Considering the Implications of Both Traditional Drug and Vaccine Access Pathways on Access and Uptake Impact

	Function /	Patient Coverage /	Patient Access /	Provider Impact /	Public Health Impact /
Vaccine	Confers immunity	Guaranteed coverage and access without OOP under the ACA and VFC program	No OOP improves access	ACIP recommendations guide timing and setting of provider administration	Increases in vaccine uptake can reduce overall burden of infectious disease and increase public health
Drug	Cures or treats an infectious disease	Coverage varies by plan type; OOP costs vary by plan type	Variable OOP and coverage may result in varied uptake	Professional society guidelines inform provider administration; potential non-coverage could discourage timely administration	Targeted to individual conditions and subject to potential UM; limited public health impact as health benefit realized in individuals

Though RSV remains one of the most common childhood infections, impacting nearly all children by the age of 2 and between 75,000 to 125,00 of them hospitalized each year, no vaccine for the disease has been approved. Furthermore, RSV is the leading cause of infant hospitalizations in the US, with a rate 16 times greater than that of influenza, and is also responsible for up to 400 deaths per year in infants under the age of 1 year.[10,11] RSV vaccine development, ongoing for more than 50 years, has faced several roadblocks throughout the development lifecycle. However, several RSV mAbs have advanced through clinical trials, including an already licensed mAb, over the last decade and may ultimately shift the market upon licensure.

While RSV vaccine development has faced substantial roadblocks over the last 50 years, several vaccine-like candidates are nearing launch and are likely to be indicated for broad use in the infant population. [12]

Similarly, researchers have worked to develop novel HIV prophylactic products for decades. Milestones have been observed, including the publication of Phase I trial data showing positive immune responses in humans, but no vaccine has been successfully developed to date. Researchers have also made significant advancements in the development of other preventive, vaccine-like, biologics, with at least 6 HIV mAbs currently in Phase I clinical trials.

In 2017, the Centers for Disease Control and Prevention (CDC) reported over 1,700 cases of HIV in adolescents aged 13-19, and a rate of 6 cases per 100,000 people, demonstrating the public health need for innovative preventive products that are currently in the pipeline.[13] Though the target populations or likely indications of pipeline HIV mAbs are not yet known, expanding access to preventive HIV products beyond already-licensed PrEP products could significantly reduce rates of HIV transmission among younger populations.

As the pipeline further expands to include vaccine-like products, pathways for patient access to such products are more complex. US policies and public health programs reflect an approach that guarantees access to vaccines in the commercial and Medicaid expansion markets, particularly for infants and children. Pediatric populations unable to access the products described above in the same way they do vaccines may face barriers and disparities to access. Unlike for vaccines, coverage for novel vaccine-like prophylactic products will depend heavily upon the dynamics of a patient's individual health insurance, creating a wide array of potential

[10] Zhou H, et al. Clin Infect Dis. 2012;54(10):1427-1436
[11] Thompson WW, et al. JAMA. 2003;289(2):179-186
[12] Mazur, Natalie I., Deborah Higgins, Marta C. Nunes, José A. Melero, Annefleur C. Langedijk, Nicole Horsley, Ursula J. Buchholz et al. "The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates." The Lancet Infectious diseases 18, no. 10 (2018): e295-e311.
[13] CDC. Diagnosis of HIV Infection Among Adolescents and Young Adults in the US and 6 Dependent Areas 2012-2017. Available here.

barriers. Such barriers could impede wide uptake of vaccine-like products, and potentially widening health disparities, limiting their impact on public health.

Current Vaccine Access for Drugs May Not Ensure Optimal Access to Vaccine-Like Products

Coverage and access for already-licensed vaccine-like products more closely resembles that of traditional drugs, rather than vaccines. Coverage, access, and patient out-of-pocket (OOP) exposure for these products depend upon several factors, including payer use of utilization management (UM), setting of administration, and the dynamics of individual insurance plan benefits, leading to significant variability across plans and markets.

Commercial Market

Coverage

Although Section 2713 of the Public Health Service Act (PHSA) requires non-grandfathered group health plans and issuers in the group and individual markets to cover immunizations for routine use in children and adolescents that have in effect an ACIP recommendation, the same coverage requirements do not apply to traditional drugs. Without an ACIP recommendation, coverage of vaccine-like products may vary by beneficiary health insurance plan, which are not required to cover all traditional drugs.

Utilization Management

Payers have also imposed UM techniques for vaccine-like products by implementing policies aligned with professional guidelines rather than the Food & Drug Administration (FDA) label, limiting coverage to select populations.[14,15] "Reasonable medical management" including prior authorization, may be permissibly applied to vaccine-like products and may present barriers to access for patients.[16] For example, payers have implemented prior authorization, covering the product only when it is administered in accordance with specialty society guidelines and administered during the RSV season.

Individual Benefit Design and Patient Out-of-Pocket

Patient access and OOP exposure similarly depend on specific benefit design and product coverage under the medical or pharmacy benefit. In the commercial market, deductibles impact patient OOP costs for drugs as enrollees are responsible for greater cost sharing before they meet their plan's deductible. Copay and coinsurance amounts depend on a beneficiary's plan type and benefit structure, as well as where the beneficiary is in their benefit utilization.[17]

[14] American Academy of Pediatrics, "Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection". Volume 135, no. 2 (August 2014). Available here.
[15] United Healthcare. "SYNAGIS® (PALIVIZUMAB)". (July 2019). Available here.
[16] 29 CFR § 2590.715-2713 - Coverage of Preventive Health Services. Available here.
[17] Kaiser Family Foundation. "2019 Employer Health Benefits Survey". (September 2019). Available here.

Among commercially insured patients, cost sharing can vary across inpatient and outpatient settings of care.[18] Clinical guidelines, set by professional societies like the American Academy of Pediatrics (AAP), often inform standards of care and are likely to do so for pipeline mAbs indicated for use in infants. Standards of care which call for at-birth administration are thus likely to promote product administration in inpatient settings. As a result, these products are more likely to be included in newborn bundled payments, potentially reducing patient exposure to additional OOP costs. Without inclusion within a standard of care and in the absence of adequate reimbursement, there may be a financial disincentive for hospitals to administer vaccine-like products at birth, moving patients to an outpatient setting for administration.

Figure 3 – The Setting of Administration for Vaccine-Like Products May Have Implications for Access and Patient OOP Costs

	Coverage & Payment	UM	Cost Sharing
Inpatient Considerations	• Standards of care which call for at-birth administration are likely to promote product administration in inpatient settings.	• Payers have also imposed UM techniques for vaccine-like products by implementing coverage policies aligned with professional guidelines.	• Cost sharing will vary by specific benefit design; plan-specific OOP max considerations will apply in the commercial market.
Outpatient Considerations	• Commercial coverage in an outpatient physician office setting will depend on the specific benefit design of an individual's plan and product coverage under the medical or pharmacy benefit.	• Payers can impose utilization management techniques, including prior authorization and step therapy.	• Cost sharing will similarly depend on specific benefit design and product coverage under the medical or pharmacy benefit.

Commercial coverage in an outpatient physician office setting will depend on the specific benefit design of an individual's plan and product coverage under the medical or pharmacy benefit.[19] Should these products be administered during a physician visit following birth, their administration may be unlikely to be included in the wellness visit but rather billed separately.[20] Separate billing may result in higher OOP costs for the patient, creating additional barriers to access and reducing overall uptake.

Medicaid Markets

Coverage

[18] Kaiser Family Foundation. "2019 Employer Health Benefits Survey". (September 2019). Available here.
[19] Id
[20] Cigna. "Well-Child Visits". (2019). Available here.

Medicaid coverage may also vary by setting of care. In exchange for Medicaid coverage and inclusion in the Medicaid Drug Rebate Program (MDRP), manufacturers must provide mandatory federal rebates for all FDA-approved drugs delivered in the outpatient setting. While the MDRP governs coverage and rebate requirements for all FDA-approved drugs in the outpatient setting, it does not apply to inpatient care delivery. This is particularly important for products that may be administered at-birth in inpatient settings of care, as Medicaid may not be required to cover them.[21] Coverage and cost sharing for Medicaid beneficiaries will depend on a variety of factors, including the establishment of updated standards of care under professional guidelines and the setting of administration.

Utilization Management

While states are prohibited from excluding outpatient drugs for children included in the MDRP, they may still apply utilization management in specific situations.[22] Implementing utilization management is likely to be influenced by the existence of other comparable market entrants indicated for prevention of the same disease in similar target populations and may reduce patient access to vaccine-like products.

Individual Benefit Design and Patient Out-of-Pocket

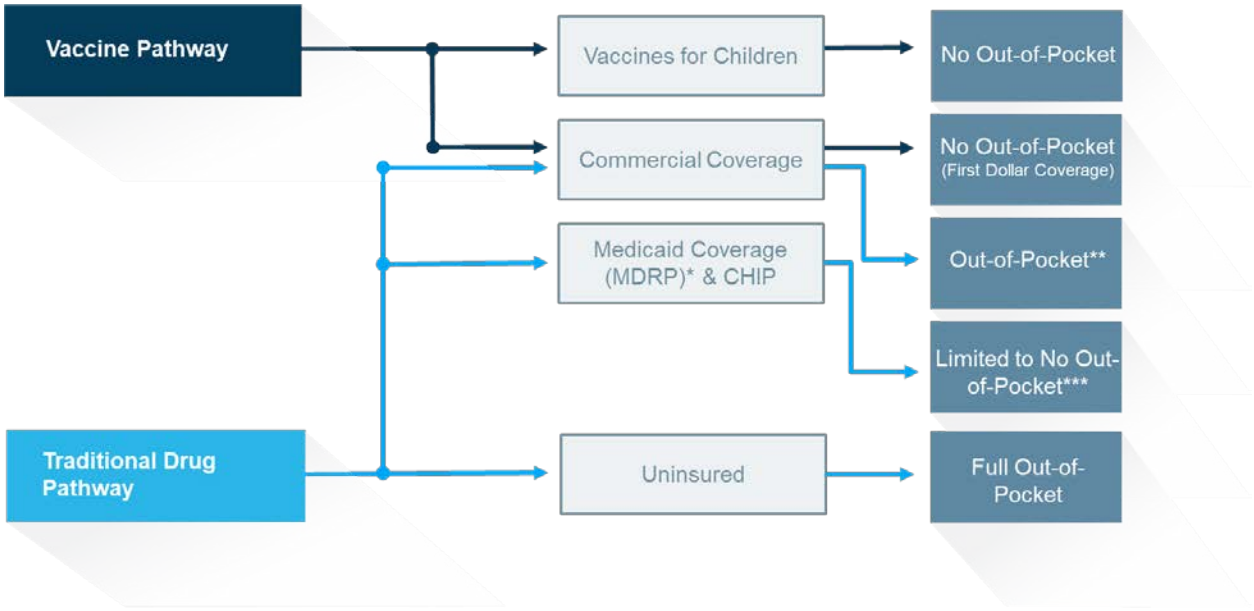
Medicaid beneficiaries will rarely bear OOP costs. In the inpatient and outpatient settings, children in Medicaid and the Children's Health Insurance Program (CHIP), which provide the Medicaid benefit package for children, do not accumulate OOP costs. Standalone CHIP programs, which are separate from Medicaid and provide benefits in accordance with a benchmark, may impose cost sharing up to 20% of the cost for a service. However, annual aggregate costs for all cost sharing cannot exceed 5% of family income.[23]

Assessing Vaccine-Like Products Under a Vaccine Pathway

In contrast to the drug coverage and access pathway described above, the vaccine access pathway differs in several important ways, including the role of ACIP and CDC. Across markets, the federal government has removed barriers to ensure broad access to vaccines, largely eliminating OOP considerations and thereby increasing uptake. In addition to the VFC, which provides access to vaccines at no cost for children, Section 2713 of the Public Health Service Act (PHSA) prohibits cost sharing for ACIP-recommended vaccines in the commercial and Medicaid expansion markets and ensures children and adults receive vaccines at no cost. Policies such as Section 2713 and VFC create a straightforward coverage and access pathway for vaccines that seek to maximize access and associated uptake of vaccines.

[21] 42 U.S.C. § 1396o
[22] 42 USC 1396r-8
[23] 42 U.S.C. § 1396o

Figure 4 – Vaccine Access Pathways Have the Potential to Increase Coverage and Reduce OOP for Vaccine-Like Products



*Products administered in-patient are not eligible for inclusion in the MDRP
**Individuals will be subject to varying benefit structures
***Per federal statute, Medicaid, and Medicaid Expansion CHIP exempts all services for children from cost sharing. CHIP may impose cost sharing up to 20% of the cost for a service, though there is an annual cap based on family income

Commercial Markets

Under section 2713 of the PHSA, as amended by the ACA, commercial plans must provide coverage without cost sharing for all immunizations for routine use in children and adolescents and which have, in effect, a recommendation from the ACIP. Regulation implemented by Health and Human Services narrowed the scope of ACIP-recommended vaccines to be covered at first dollar to those included on the ACIP Immunization Schedules.

This pathway, however, does not currently include coverage of vaccine-like products, as exemplified by the hepatitis B IgG. Historically, ACIP has not evaluated vaccine-like products, including Igs and mAbs for its recommended vaccine schedule, though ACIP has issued recommendations for use of several Igs in conjunction with vaccines. The hepatitis B IgG, a preventive biologic given to infants born to HBsAG-positive mothers or others at high risk for hepatitis B virus infection, is excluded from first-dollar coverage, while the hepatitis B vaccine, recommended for all infants, qualifies for first-dollar coverage.

Because products like the hepatitis B IgG are covered and accessed like traditional drugs and are not added to the infant immunization schedule, children with commercial insurance coverage may face variable and uncertain coverage for these products, which may hinder access and uptake. Should vaccine-like products, which serve similar functions as the hepatitis

B IgG, be added to ACIP's infant and childhood immunization schedule, they would receive first-dollar coverage under the PHSA and would be made available to infants and children without cost sharing.

Medicaid Markets

Separately, because Medicaid vaccine coverage requirements apply for the hepatitis B vaccine, children enrolled in Medicaid and Medicaid Expansion CHIP programs are entitled to full Early and Periodic Screening, Diagnostic, and Treatment benefits, including vaccines purchased through VFC. As described, Medicaid-eligible and uninsured children are also guaranteed access with no cost sharing because the hepatitis B vaccine is included in the VFC program. While children enrolled in standalone CHIP programs are not eligible for VFC, states are required to cover vaccines as a condition of their annual federal CHIP allotment, which ensures access for low-income children. If such products were to be added to ACIP's immunization schedule, the Committee may also consider its inclusion in the VFC program, which would secure broader access for underinsured and uninsured pediatric populations. Overall, the vaccine pathway ensures access across the Medicaid market, minimizing gaps in vaccine administration and eliminating the risk of children missing doses due to cost.

For pediatric products administered at birth, hospital-based administration can introduce several additional considerations. Hospital bundling may disincentivize at-birth administration of products without a requirement for plans to cover due to cost. Because the hepatitis B vaccine birth dose is administered at the hospital, the vaccine can be instructive for other pipeline products that require similar administration. ACIP-recommended products are required to be covered without cost sharing eliminating the concern that cost sharing would disincentivize administration. An ACIP recommendation for a vaccine-like product indicated for use at birth could increase administration in the hospital setting and may increase overall patient access.

Expanding current vaccine policies and public health programs to include vaccine-like products may increase patient access to products similar to the hepatitis B IgG in the same way they access hepatitis B vaccine. Applying these policies to vaccine-like products could help remove the barriers patients will face in trying to access the products to realize their full public health benefit.

Conclusion

Like vaccines, novel non-vaccine prophylactic products can prevent infectious disease. Current policy frameworks for vaccines do not contemplate the existence or role of these "vaccine-like" products in increasing public health protection. Under the status quo, vaccine-like products are not likely to be accessed through the vaccine pathway, which may increase patient OOP costs,

lead to lower levels of coverage by payers, and may create disparities in coverage and sub-optimal incentives for provider to administer in inpatient settings of care.

An ACIP recommendation and inclusion on public health programs, like VFC, may result in coverage for vaccine-like products similar to existing vaccines. Without a recommendation or inclusion in VFC, such products are more likely to be covered and accessed like traditional drugs, which may be more variable from health insurance plan to plan and across both public and private systems of health insurance. The current system for vaccine coverage, by virtue of no or low OOP costs, is designed to increase patient access and reduce the incidence of infectious disease. Replication of existing vaccine coverage and access mechanisms for vaccine-like products, particularly given their shared preventive characteristics, may increase patient access, reduce disparities, lower OOP costs, and reduce the public health burden of childhood diseases, as it has measles.

Stakeholders evaluating the potential public health impact of vaccine-like products may benefit from considering the implications of both pathways for coverage and access. Should vaccine-like products be covered and accessed like traditional drugs, patients may face increased coverage variability, which in turn, could increase health disparities between those who can access such products and those who face access challenges. As the pipeline of vaccine-like products grows, expanding coverage and access policies to accommodate them without patient access barriers, will help facilitate their broad public health impact.

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