Intervention Demand Forecasting

A BMGF Guide

BILL & MELINDA GATES foundation

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Introduction

DOCUMENT PURPOSE

The purpose of this document is to help program teams understand the demand forecasting approach used by the Bill and Melinda Gates Foundation so they can leverage BMGF-approved and expert-vetted methodologies when developing demand forecasts. Given a demand forecast is only as good as its inputs, this document also provides perspective on how to develop credible input assumptions for the most critical demand forecasting variables.

The methodologies and guidelines presented in this document are intended for use when developing a demand forecast to support strategy development or major investment decision-making[1]. These strategic demand forecasts (SDFs) will generally be developed for products that have not yet reached market, that are typically several years from launch, and require a forecast spanning a time horizon of >10 years. The further from market, the more uncertain the forecast, however, SDFs are intended to be approximate estimates of product demand.

BACKGROUND

This document describes methodology and guidelines that form the Foundation's framework for developing a strategic demand forecast. There is no universal method for developing a demand forecast. The methodology and input assessment criteria presented herein were developed in partnership with BMGF and are in line with other internal initiatives concerned with demand forecasting and product development, such as the Integrated Portfolio Management (IPM) project. This guide has been vetted with internal and external global health experts. The content may not be appropriate for every demand forecasting scenario and BMGF grantees and partners may choose to use their own demand forecast methodology.

This document is not intended to be a step-by-step instruction manual for conducting a demand forecast or designing and building a forecasting model, but instead should serve as a methodological overview and companion guide for developing demand forecasts. Methods and content are presented by intervention type and are not specific to any particular disease or product. However, examples provided throughout the document draw on disease and product specific experience.

To develop a demand forecast, data and assumptions will be incorporated from various sources. These may include un-published and confidential information provided to the Foundation by partners, such as Product Development Partners (PDPs) and manufacturers. Care should be taken to ensure that confidential information is not shared with other third parties outside of the Foundation and to ensure compliance with existing confidentiality and non-disclosure agreements.

This document is currently an internal document and is not meant to be shared with parties outside the Foundation. It is intended to be a "living document." Changes and additions should be made as the content described is applied to specific demand forecasting analyses. Changes can incorporate the Foundation's specific experience, including tips and additional data sources and assumption criteria that are encountered in real-world application of this methodology, as well as potentially incorporating standard BMGF assumptions or history-based benchmarks.

[1] As opposed to supply-chain forecasts which are more operational in nature and inform inventory and production scheduling, financial planning, and sales strategy. Supply-chain forecasts are generally conducted for products in or close to market and typically cover a 12-month to 3-year time horizon. Supply chain forecast accuracy is supported by availability of predictive data (usually recent past consumption) and short feedback cycles.

DOCUMENT SCOPE AND ORGANIZATION

The first step in developing a demand forecast is to be very clear on what the forecast represents. For example, Figure 1 identifies the types of forecasts generally referred to as "demand forecasts." Forecast developers often misuse forecast language which can result in misinterpretation of the results.

Figure 1: Demand Forecasting Tiers

Market Need represents the number of subjects or patients who would benefit from an intervention if it were available to them. Market need is independent of a specific product, but rather represents the total demand for a disease-altering intervention based on the disease burden.

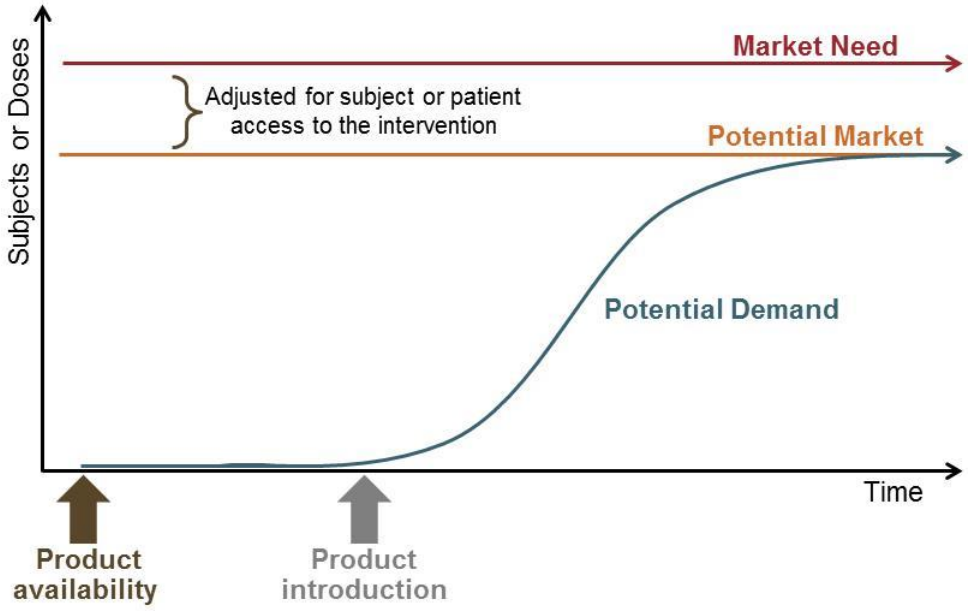
The ***Potential Market*** represents the number of subjects or patients who would benefit from an intervention and who will have access to the intervention. In the case of a vaccine intervention, this would be the percent of subjects that could be vaccinated (i.e., coverage rate) given a country's immunization program infrastructure. Because not all subjects or patients will have access to all health interventions, the potential market will always be smaller than the market need.

The ***Potential Demand*** is the demand for an intervention or group of interventions, given availability, the countries that choose to introduce the intervention(s), and the time it takes countries to reach peak intervention usage. The potential demand assumes no supply or financing constraints. This constraint-free forecast enables us to understand the total demand if supply and cost were not an issue. Although it does not include supply and demand dynamics, it will convey the amount of supply required to meet demand and when that supply will be required. This, along with an understanding of the current supply landscape, will provide insight on potential supply investment needs. Although it does not include financing impact on demand, it will convey the level of funding required to meet the potential demand, given intervention procurement and delivery costs. This too will help inform decision-making with regard to introduction ability and the level of funding or fundraising required.

Forecasted Demand is the potential demand adjusted for supply and financing constraints and typically captures the expected product allocation and competitive landscape dynamics over time.

Figure 2 illustrates the key distinctions between market need, potential market and potential demand. The focus of this document is the development of ***Potential Demand Forecasts***.

Figure 2: Relationship of Potential Demand to Potential Market and Market Need



The input assessment criteria for the potential demand forecasts described in this document do not include supply and financing considerations. However, if information on these constraints is available, the forecast developer is encouraged to document the information so it too can help inform investment decision-making and the assessment of forecasted demand.

This document is organized by intervention type. Each section details the methodology for conducting a potential demand forecast for the listed intervention. It then reviews the criteria for making input assessments for the critical forecast variables. Table 1 summarizes the intervention scope addressed in this document.

The methodology and content presented herein does not account for any cross-intervention interactions, for example, an increasing vaccine product demand ultimately leading to a decreased demand of drug treatments for the same disease. These types of interactions require more complex and interrelated methodology that is often specific to the characteristics of a particular product or products. Cross-intervention interaction is discussed further at the end of this document.

Table 1: Guidelines Document Intervention Scope

Intervention Type	Definition
Vaccine	Product or product candidate that induces an immune response to prevent a disease or disease subtype in non-infected subjects
Drug Treatment	Product or product candidate that treats a disease or disease subtype
Prevention Drug Treatment	Product or product candidate that reduces the risk of disease or disease subtype in non-infected subjects
Prevention Device	Product or product candidate that reduces the risk of a condition, disease, or disease sub-type
Diagnostic	Product or product candidate that identifies or confirms a specific condition or disease

Vaccines

VACCINE PRODUCT STRATEGY

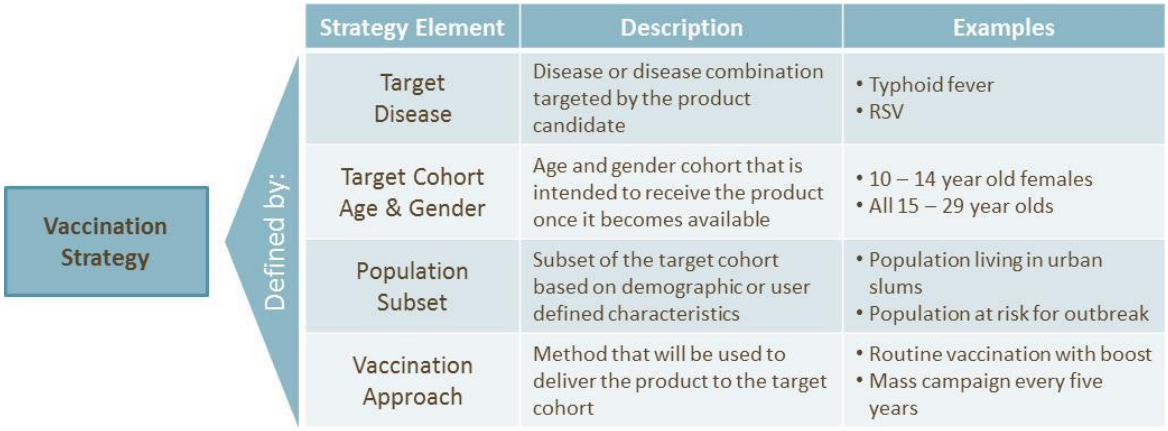
Potential demand can be forecasted for a single vaccine product or product candidate or a group of vaccine products or product candidates targeting the same disease and population. For example, if there is only one product candidate in development for a particular disease and population, the demand forecast will of course represent demand for that specific product candidate. If there are multiple product candidates in development (e.g., three rotavirus vaccines from different suppliers), all targeting the same disease and population with the same vaccination approach, then the potential demand forecast would represent demand for the group of product candidates (e.g., rotavirus vaccine demand). In this case, the demand represents the total demand for all candidates.

When forecasting demand for multiple product candidates targeting the same disease and population with the same vaccination approach, demand for each individual product candidate can be determined if the forecaster chooses to assess each in-scope country's product preference. Information to consider when assessing country product preference will be discussed at the end of this chapter.

To forecast potential demand, every product candidate or group of product candidates will need a clearly defined vaccination strategy that will inform where, who, and how to vaccinate against a specific disease or diseases. The vaccination strategy must include a target population cohort (who to vaccinate) for the specified disease or disease combination and a vaccination approach (where and how to vaccinate). Each in-scope country's demand for a specific vaccination strategy contributes to the overall demand for that vaccination strategy.

When defining a vaccination strategy, four key elements need to be specified. Figure 3 describes these four elements.

Figure 3: Vaccination Strategy Elements



Strategy Element	Description	Examples
Target Disease	Disease or disease combination targeted by the product candidate	• Typhoid fever • RSV
Target Cohort Age & Gender	Age and gender cohort that is intended to receive the product once it becomes available	• 10 – 14 year old females • All 15 – 29 year olds
Population Subset	Subset of the target cohort based on demographic or user defined characteristics	• Population living in urban slums • Population at risk for outbreak
Vaccination Approach	Method that will be used to deliver the product to the target cohort	• Routine vaccination with boost • Mass campaign every five years

Through the specification of these four elements, any vaccination strategy can be defined.

Vaccination Strategy Examples

- Routine vaccination of all infants for Pneumonia
- Routine vaccination of infants in high risk areas with a one-time catch-up campaign in 1 – 15yo for Japanese Encephalitis
- Periodic mass campaign of 1-15yo in urban slums and rural areas without access to clean water for Cholera
- Routine vaccination of all 10yo with a boost every 10 years for Tuberculosis

Vaccination strategy information, and other important demand forecasting-related information, can be found in the product candidate's Target Product Profile (TPP) and Integrated Product Development Plan (IPDP). The information gathered from these documents should include, at a minimum, the data highlighted in Table 2.

Table 2: Potential Sources of Vaccine Candidate Information

Target Product Profile	Integrated Product Development Plan
• Indication • Target population (e.g., age, gender) • Presentation and formulation • Route of administration • Dosing schedule • Efficacy • Duration of protection • Storage requirements	• Current product candidate status • Development phase start date and duration • Estimated date of prequalification

The target population cohort will be a specific age group and may also be gender-specific or target a particular sub-population. Once defined, the target population data by country can typically be sourced from the following reference data:

- UN World Population Prospects (revised annually)
- World Bank, HNP Database Population Projections (revised annually)
- Other data source, as appropriate (e.g., subnational population data, % of population at risk)

POTENTIAL VACCINE DEMAND FORECASTING METHODOLOGY

The methodology presented in this document is focused on the potential demand for a single vaccine product or group of like products delivered via a specified vaccination strategy. The potential demand forecast will be developed through a series of calculations. Each calculation requires a set of key input assumptions that should be clearly documented and transparent to those interested in the demand forecast. Table 3 identifies the calculation components and the key inputs required for each calculation.

Table 3: Vaccine Calculation Components and Input Requirements

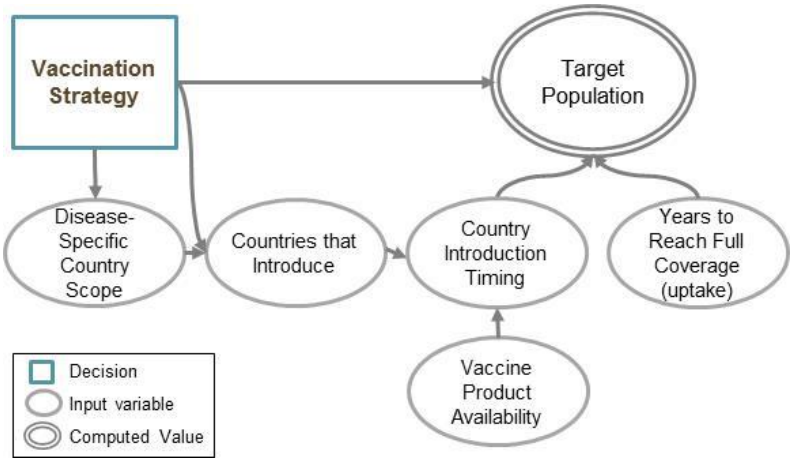
Calculation Component	Input Requirements
Target Population(s)	• Disease-specific country scope • Countries expected to introduce the vaccine • Vaccine product availability • Country introduction timing • Country vaccine preference (if appropriate) • Vaccine uptake pattern
Number of Fully and Partially Immunized Subjects	• Dose by dose vaccination coverage rate of the primary vaccination series
Number of Fully and Partially Boosted Subjects	• Boost by boost vaccination coverage rate of the boost vaccination series
Doses Demanded for Immunization	• Doses required per fully immunized subject (primary series) • Boosts required per fully boosted subject
Doses Required to Cover Wastage	• Wastage rate (%)
Doses Required for Buffer Stock	• Buffer stock (%)

This document will use simplified "influence diagrams" to provide a step-by-step demand forecasting guide. Each section will highlight a piece of the overall influence diagram to help guide the reader through a section at a time. The complete influence diagram will be provided at the end of the vaccine intervention chapter. Within all influence diagrams, the single lined bubbles represent the input variables that must be assessed in order to develop the potential vaccine demand forecast. Double-lined bubbles represent calculations (e.g., adding or multiplying two or more input variables).

Target Population Forecast

Figure 4 represents the input variables required to forecast the target population(s) over time. Five input variables are required to forecast the target population for a specific vaccination strategy.

Figure 4: Target Population Forecast



Disease-Specific Country Scope

The disease-specific country scope defines which countries should be included in the potential demand forecast. The country scope should be determined based on disease burden. The country scope may include all countries if the disease is global in nature (e.g., pneumonia, rotavirus) or a specific set of countries if the disease is regionally focused (e.g., typhoid, Japanese encephalitis). Many disease burden sources will identify the highly endemic countries for a given disease, so disease-specific country scope assumptions are not typically considered highly uncertain or difficult assumptions to make.

Countries That Introduce

Not all countries with measurable disease burden will choose to introduce a particular vaccine. Different factors may influence whether a country actually introduces a new vaccine into its national immunization program.[2,3] Countries may have other healthcare priorities, may be distracted by critical sociopolitical issues, or may not know their true disease burden. Therefore, the forecaster will need to identify which of the in-scope countries are actually expected to introduce the vaccine within the forecast timeframe. Although more of an art than a science, defining the countries that are actually expected to introduce is not typically considered a highly uncertain or difficult set of assumptions to make.

Vaccine Product Availability

If a country is expected to eventually introduce a vaccine product, the earliest possible introduction date is dependent on the availability of the product. A vaccine product is considered available when it has been licensed by a National Regulatory Authority (NRA). This first licensure status does not imply that any country can introduce at

[2] World Health Organization. Principles and considerations for adding a vaccine to a national immunization programme: from decision to implementation and monitoring. , 2014.

[3] GAVI. GAVI Country Eligibility. 2014.http://www.gavialliance.org/support/apply/countries-eligible-for-support/.

that time given a country must satisfy its own regulatory requirements before introduction can occur. Therefore, the vaccine product availability assessment sets the earliest date by which a vaccine product can be introduced into a country.

Because vaccine product availability is dependent on the successful execution and timing of the product development plan and the successful completion of supporting activities (e.g., manufacturing scale-up), the timing for product availability can be highly uncertain. Comparing development plan timing assumptions to appropriate benchmarks or similar plans that have already been completed can sometimes help mitigate some of the assessment uncertainty. Accounting for uncertainty by assessing timing ranges for each activity to enable a probability-weighted timing assessment can also help capture the uncertainty associated with product availability.

Country Introduction Timing

A vaccine product cannot be introduced until it has been licensed by a country's own NRA or by another acceptable NRA. For some countries (e.g., GAVI-eligible countries, countries procuring through UNICEF), country introduction is dependent on a product receiving WHO prequalification. Because product availability can be uncertain, introduction timing methodologies typically define introduction in terms of years from first available product. By taking this approach, the introduction timing will shift appropriately if the product availability assessment is modified.

Even though a vaccine product may be eligible for introduction, the actual timing of county introduction is dependent on many other factors. Table 4 identifies some of the more common factors that influence country introduction timing.

Table 4: Common Factors that Influence Country Vaccine Introduction Timing

Country Vaccine Introduction Timing Factors
• Disease burden • Economic status • Sociopolitical unrest • Country health system and immunization program • Competing priorities • Vaccine adoption history • Vaccine efficacy and duration of protection • Vaccination strategy

Disease Burden

Disease burden can be a major influencer of country introduction timing. The greater the burden, the more likely a country will introduce if there are no other confounding issues. The greater the disease impact, the earlier a country is likely to introduce, although exceptions to this rule are notable (e.g., India). Country-specific disease burden data can be obtained from a variety of sources (e.g., WHO, IHME). Although each source has its believers and detractors, using the same source whenever possible will mitigate differences based on disease burden methodologies alone.

Economic Status

When examining historical vaccine introduction data, countries with lower economic status tend to be later adopters of new vaccines. This assumption has been challenged with time, as more recent data has shown that GAVI-eligible LMICs introduce vaccines more quickly than non-GAVI-eligible LMICs. Classification of countries by GAVI-eligibility and GDP or GNI can be a useful way to group countries into different introduction timeframes.[3,4]

Sociopolitical Unrest

[4] World Bank. World Bank country classifications. 2014.http://data.worldbank.org/country.

Countries experiencing significant civil or political unrest (e.g., Somalia) will typically be slower adopters of new vaccines than countries with stable social and political systems.

Country Health System and Immunization Program

Understanding whether a country's health systems or immunization programs are improving, or are in a state of stagnation or decline, can be helpful for determining country introduction and introduction timing. Country-specific vaccine coverage rates can also be a useful indicator, as countries with low coverage rates may not have strong enough immunization systems to support additional vaccine introductions. Other factors to consider include healthcare workforce capacity and experience, current cold chain capacity, and disease surveillance system status.

Competing Priorities

A country's willingness to introduce a new vaccine may be influenced by competing healthcare priorities. If multiple new interventions are available in relatively the same timeframe, a country may choose to introduce the intervention that addresses the highest disease burden or unmet medical need. The decision may also be influenced by political will or availability of external funding. Understanding the intervention choices a country will likely have over a 3-5 year timeframe will help guide country introduction timing estimates.

Comprehensive multi-year plans (cMYPs[5,6]) may also be a helpful source for assessing a country's vaccine introduction and timing plans.

Vaccine Adoption History

Understanding historic vaccine introduction timing relative to when each vaccine was available may also help inform future vaccine introduction timing. Countries that have been early adopters are likely to remain early adopters. Countries that have been late adopters are likely to remain late adopters. However, before assuming historic behavior will indeed continue, considerations that may change historic trends should be examined (e.g., change in leadership, change in sociopolitical status).

Vaccine Efficacy and Duration of Protection

Vaccine efficacy and duration of protection can influence country introduction decision-making. A country may determine a product is not cost-effective because of a lower than desired efficacy or a short duration of protection. While formal cost-effectiveness analyses are helpful for informing vaccine introduction timing, they may not be available for all interventions under consideration.

Vaccination Strategy

A country may choose not to introduce a vaccine product if its vaccination strategy is perceived to be incompatible with a country's immunization program strategy or budget. For example, a vaccination strategy requiring frequent re-vaccination of the target population cohort (e.g., mass campaigns in 5-15yo every three years) may not be feasible from a logistics or a budget standpoint.

Country introduction timing assessments are perhaps the most difficult of all the demand forecasting input requirements due to the many factors that influence if and when a country will introduce a particular vaccine product. Because of the importance of this assessment, the forecaster should obtain and document as much information as possible.

[5] World Health Organization. Country Planning Cycle Database. 2014.http://www.nationalplanningcycles.org/.

[6] World Health Organization. WHO Comprehensive Multi-Year Plans (cMYP). 2014.http://www.who.int/immunization/documents/control/WHO_IVB_14.01/en/.

Country Vaccine Introduction Information Sources

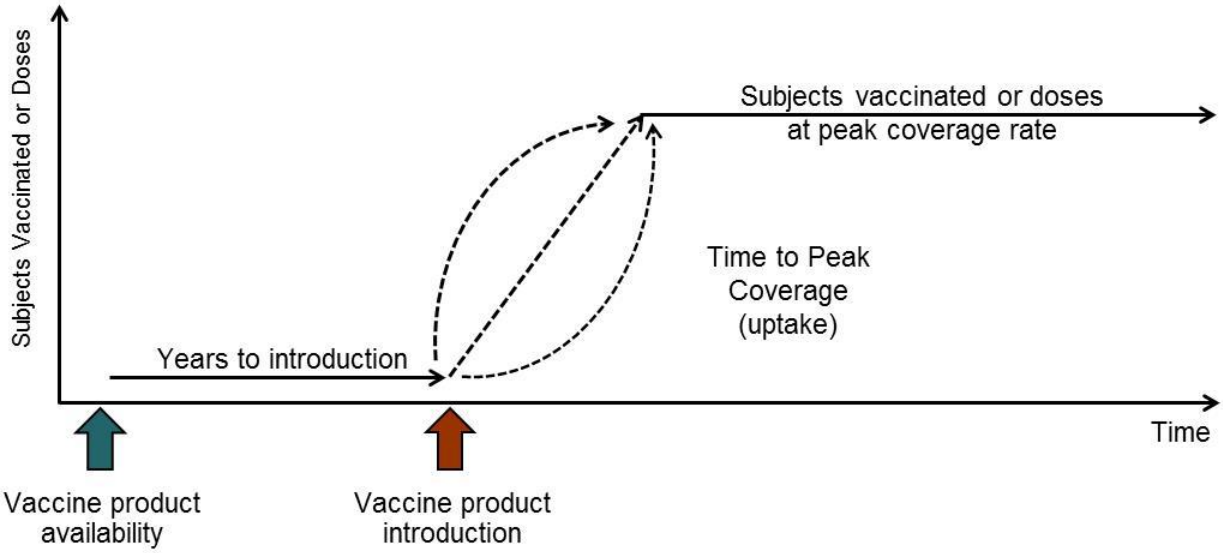
Potential sources of country introduction timing information include:

- GAVI Strategic Demand Forecasts
- WHO New Vaccine Introduction Database (historic information)
- Vaccine Investment Cases (e.g., Cholera)
- PDP demand forecasts (e.g., Aeras, MVI, IVI)

Years to Reach Full Coverage (uptake)

The final assessment required for determining the target population over time, is the vaccine product's uptake pattern post introduction. The uptake pattern essentially defines the number of years required to reach peak vaccination coverage and whether the uptake is linear or non-linear over time. The vaccine product uptake pattern is influenced by country size and vaccination strategy. Once new products are introduced, smaller countries typically take less time to reach peak coverage than larger countries. For uptake timing purposes, countries are typically categorized as small, medium, large, or very large. The global health sector (i.e., GAVI) has benchmarked time to peak coverage based on this size categorization. As always, exceptions have been identified (e.g., India). The typical framework for assessing uptake is illustrated in Figure 5.

Figure 5: Vaccinated Subject Forecast

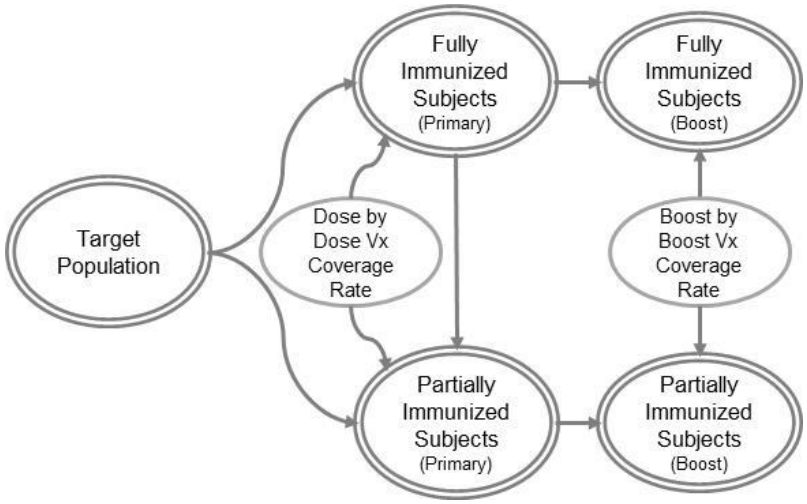


Fully & Partially Immunized Subjects Forecast

The target population forecast and the dose by dose vaccination coverage rates for both the primary and boost doses, if applicable, are inputs to the forecast of fully and partially immunized subjects. Capturing the demand required to fully immunize subjects is critical and will represent the demand that can actually deliver a health impact. While partially immunized subjects are not expected to realize the full effectiveness of the vaccine, the doses used on partially immunized subjects are important to capture for supply planning and procurement cost forecasting purposes.

Figure 6 highlights the relationship between the coverage rate-related input and output variables.

Figure 6: Fully & Partially Immunized Subjects Forecast



Dose by Dose Vx Coverage Rate (primary doses only)

The dose by dose vaccination coverage rate forecast provides an estimate of the percent of the target population expected to be immunized based on access to the product, and the subjects' adherence to the full course of treatment. For new vaccines, a vaccination coverage rate proxy is typically used for demand forecasting purposes. For example, a single dose neonatal vaccine product would use BCG coverage rates as its proxy, whereas a three dose vaccine delivered on the EPI schedule would use DTP coverage rates as the proxy. When using an existing coverage rate forecast as a proxy for a new vaccine, care must be taken to ensure the vaccination strategies are comparable.

Historic vaccination coverage rates are published annually by UNICEF and WHO. GAVI, in partnership with WHO and UNICEF, develop vaccination coverage rate forecasts for use in vaccine demand forecasts. GAVI has typically made these coverage rate forecasts available to the foundation. The most common coverage rate forecasts used as proxies for new vaccine products include:

- BCG
- DTP1, DTP2, DTP3
- MCV

If the primary product dosing schedule includes more than one dose, the coverage rate values for each dose need to be assessed. For example, the % of target population receiving the first dose; % of target population receiving the second dose; and so on. If the dose-by-dose coverage rates are not available, a cumulative dose vaccination coverage rate can be used. Cumulative dose vaccination coverage rates estimate the percent of the target population that receive all of the intended doses in the primary vaccination series (e.g., DTP3 coverage rate – the % of subjects receiving all three doses of a DTP vaccine). If dose by dose coverage rates are not available, the demand forecast will represent the demand from fully immunized subjects. This will result in an underestimate of demand given the forecast ignores those subjects who have only received a subset of the intended doses.

If a vaccine is intended for multiple age cohorts, and each cohort has a cohort-specific delivery approach (e.g., routine and catch-up campaign), coverage rate forecasts should be developed for each vaccination approach.

Boost by Boost Vx Coverage Rates

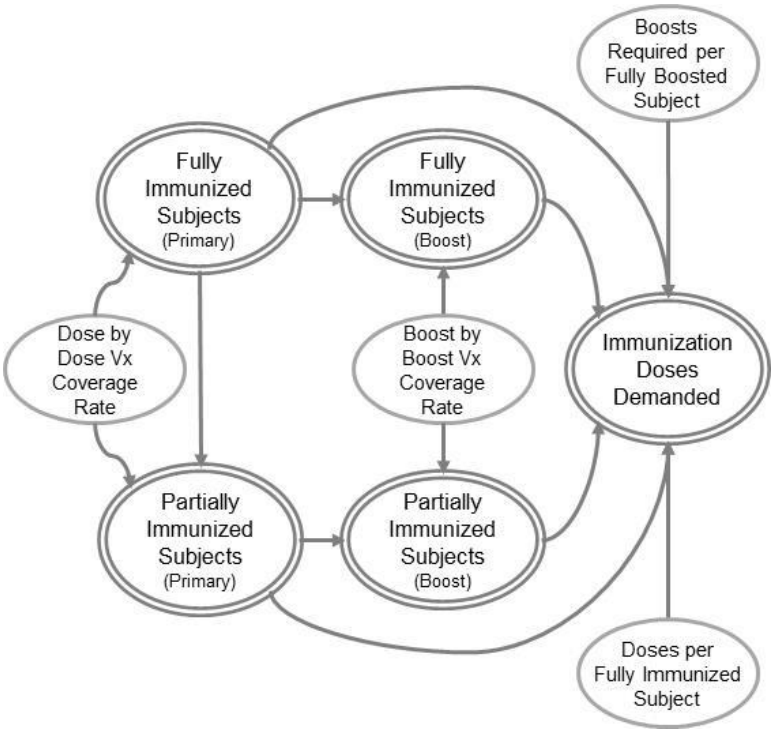
The boost by boost vaccine coverage rate forecasts estimate the percent of the fully and partially immunized population that receive each boost in the boost series. Similar to the calculations for fully and partially immunized subjects, if the boost dosing schedule includes more than one boost dose, the coverage rate values for each boost will need to be assessed.

Immunization Doses Demanded

The fully and partially immunized subjects associated with the primary and boost doses, and the primary doses and boosts required per fully immunized subject, are the basis for calculating potential demand in doses. The demanded doses forecast is determined by combining the primary and boost doses associated with the fully immunized subjects and the primary and boost doses associated with the partially immunized subjects. Figure 7 highlights the relationship between the dosing-related input and output variables.

The number of doses per fully immunized subject (primary doses) and per fully boosted subject should be specified in the product candidate's TPP. If the product being forecasted is already in-market, the dosing information will be included in the product's package insert. Whenever possible, the package insert associated with a product's WHO prequalification should be used as its information will be more relevant for developing country demand forecasting.

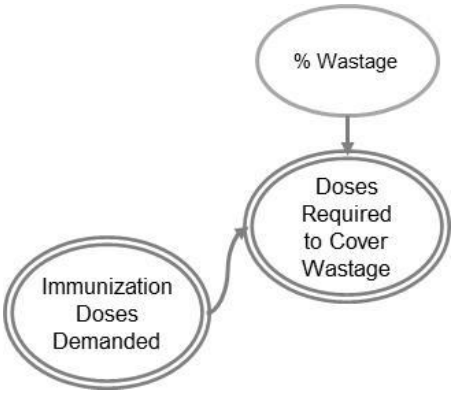
Figure 7: Doses Demanded for Fully and Partially Immunized Subjects



Doses Required to Cover Wastage

Vaccine product wastage can be significant. Therefore, it is important to account for wastage in the final potential demand forecast. Wastage is typically defined as a percentage of the doses demanded for immunization. Figure 8 highlights the relationship between wastage-related input and output variables.

Figure 8: Doses Required to Cover Wastage



The wastage rate is the percentage of demanded doses (i.e., procured doses) that will be unavailable for immunization because of losses due to lost or broken vials, partially used vials, or inadequate cold chain protection. The doses required to cover wastage is equal to the number of doses demanded divided by 1 minus the percent wastage.

Vaccine wastage rates depend on multiple criteria, but are driven primarily by the vaccine product's formulation and packaging (e.g., liquid or lyophilized formulation, vial size). WHO publishes wastage rates for products based on their formulation and presentation[7]. The rates are intended to be used as benchmarks for planning purposes.

Country generated wastage rates can typically be found in cMYPs, but these rates vary widely across countries and the estimation methodology is not well documented or understood. The global health community generally agrees the WHO wastage rates are acceptable for strategic demand forecasting and other planning purposes.

WHO Vaccination Wastage Rate Assumptions

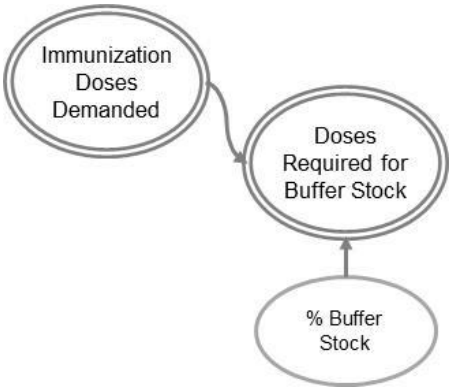
- All single dose vials are assumed to have a 5% wastage rate regardless of product formulation.
- Lyophilized vaccines:
  - 50% wastage rate for 10-20 dose vials
  - 10% wastage rate for 2-6 dose vials
- Liquid vaccines:
  - 25% wastage rate for 10-20 dose vials
  - 10% wastage rate for 2-6 dose vials

Doses Required for Buffer Stock

Buffer stock is the additional stock of vaccine kept at the country level to help avoid product stock-outs. Buffer stock provides countries with surplus doses should they be needed to meet faster than expected demand or to mitigate the impact of potential future supply shortages. Figure 9 highlights the relationship between buffer stock-related input and output variables.

[7] World Health Organization. Projected Vaccine Wastage. http://www.who.int/immunization_delivery/systems_policy/logistics_projected_wastage/en/ (accessed 5 Apr2013).

Figure 9: Doses Required for Buffer Stock



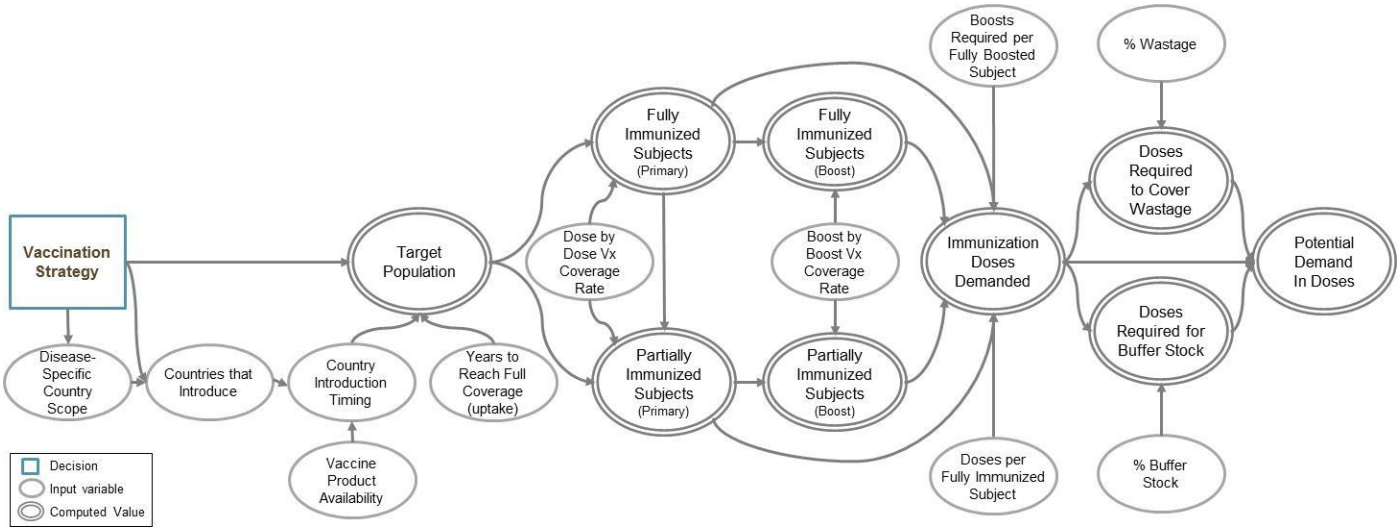
Country specific information about the amount of buffer stock procured is often difficult to find. For analysis purposes, buffer stock defaults may be set for each type of vaccination approach (i.e., routine immunization or immunization catch-up campaigns). These defaults are usually applied at the global level, that is, they are applied to all countries.

Assessments and guidelines for defining vaccine buffer stock are available from UNICEF Supply Division and GAVI.[8] For example, to ensure countries have a sufficient number of vaccine doses for routine vaccination, GAVI normally assumes a buffer stock representing 25% of a country's three month demand in any given year.[9]

POTENTIAL VACCINE DEMAND FORECASTING METHODOLOGY SUMMARY

The complete methodology for determining potential vaccine demand for a single vaccine product or group of similar products is summarized in Figure 10.

Figure 10: Potential Vaccine Demand Methodology



Because much effort over the last decade has been focused on developing best practice methods for strategic vaccine demand forecasting, significant information on how to develop a forecast can be found in published literature. It is also relatively easy to access required reference data (e.g., population cohorts, country-

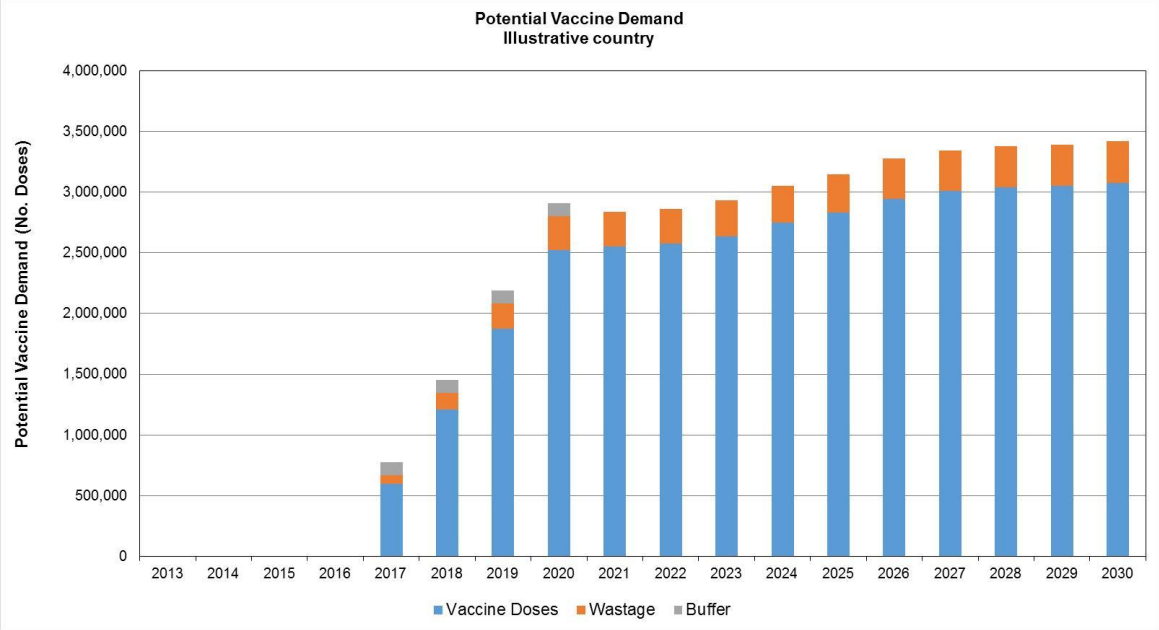
[8] UNICEF. UNICEF Guidelines to Complete the 2012–2016 Immunization Forecast Spreadsheet., 2012.

[9] GAVI. GAVI glossary. 2014. http://www.gavialliance.org/glossary/a-e/.

specific disease burden data) and assessable data input benchmarks (e.g., wastage rates, buffer stock rates) to support vaccine forecasting efforts.

Figure 11 provides an example of the potential doses demanded for a vaccine product in an illustrative country. In this example, vaccine uptake increases to that country's peak demand in 2020 in a linear fashion over four years; 25% of the required buffer stock for that country is purchased in each of the first four years; and wastage accounts for the remaining doses the country will need to procure.

Figure 11: Potential Vaccine Demand Example



FORECASTING POTENTIAL DEMAND FOR EACH VACCINE PRODUCT

As previously mentioned, potential demand can be forecasted for a single vaccine product, a group of products targeting the same disease and population, or for each product in a group of products targeting the same disease and population. In a situation where demand for multiple product candidates is required, the forecaster must determine each country's vaccine product preference. Given only one vaccine is typically used within a country to address a particular disease, the concept of defining the market share for each product within a country does not apply for vaccines. Therefore, an assessment of which vaccine product each in-scope country will prefer is required.

A country's decision to prioritize one vaccine product over another will depend greatly on the trade-offs between various vaccine product characteristics. Table 5 identifies some of the more common vaccine product characteristics that are taken into consideration when determining country product preference.

Table 5: Country Product Preference Assessment Considerations

Vaccine Product Characteristic	Trade-off Considerations
Efficacy/Effectiveness	Does one product have a more attractive efficacy/effectiveness profile than the others?
Price	Which product offers the best benefit to cost ratio?
Serotype/Strain	Does one product better address the serotypes or strains that are most prevalent in the country?
Safety Profile	Does one product have a better safety profile than the others?
Formulation/Presentation	Does one product have a more favorable formulation or presentation than the others?
Product Delivery	Does one product provide a delivery advantage over another?

Trade-offs may need to be made between various criteria depending on their relative importance for decision-making. For example, sacrificing some efficacy for a more affordable product, or choosing a more costly product because it better addresses the country's serotype/strain prevalence.

If vaccine preference is defined, the forecaster will need to develop a product allocation methodology that accounts for preference at time of country introduction. For example, if a country is expected to introduce in 2018, but its preferred product is not available until 2020, then the forecaster can allow for introduction of the lesser preferred product in the interim rather than delay introduction. If the product allocation methodology allows, the country could then switch to its preferred product once it becomes available. Likewise, the forecaster can have a country wait until their preferred vaccine is available (e.g., can't afford the early vaccine and has to wait for the lower priced vaccine). This preference setting is very important for vaccines given countries do not generally introduce multiple vaccine products targeting the same disease and population.

Drug Treatment

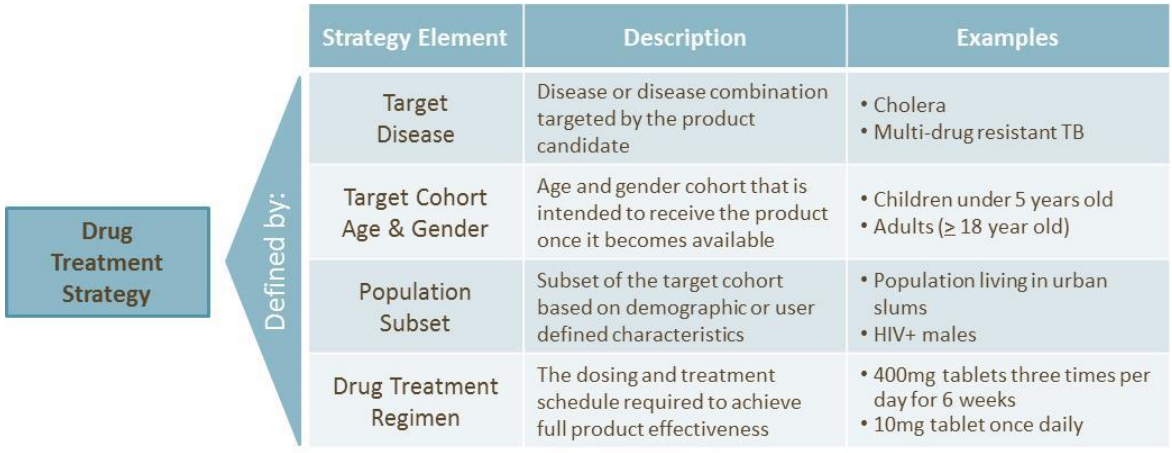
DRUG TREATMENT STRATEGY

Potential demand can be forecasted for a single drug treatment or drug combination treatment targeting a particular disease or condition. If there is only one drug candidate in development for a particular disease and target population (e.g., single dose of albendazole for all patients with hookworm), the forecast will of course represent demand for that specific drug candidate. If there is a drug candidate in development that is being tested in combination with in-market products (e.g., TB drug combination products), then the potential demand forecast would represent demand for the drug combination, not the individual drug candidates comprising the combination treatment.

To forecast potential demand, every drug candidate or drug candidate in combination with other products will need a clearly defined drug treatment strategy that will inform how and to whom the products will be delivered in the field. A drug treatment strategy is defined by its drug treatment regimen (how to treat), the associated target patient population cohort (who to treat), and the specific disease or disease combination (what to treat). Each country's demand for a candidate-specific treatment strategy contributes to the overall potential demand forecast.

When defining a drug treatment strategy, four key elements need to be specified. Figure 12 describes these four elements.

Figure 12: Drug Treatment Strategy Elements



Through the specification of these four elements, any drug treatment strategy can be defined.

Drug Treatment Strategy Examples

- Artemisinin-based combination drug treatment for uncomplicated *P. falciparum* malaria for patients, once daily for 3 days
- Isoniazid, rifampicin, pyrazinamide, and ethambutol E drug combination treatment for new, drug-sensitive pulmonary tuberculosis for patients, once daily for 2 months, followed by isoniazid and rifampicin drug combination treatment once daily for 4 months

Drug treatment strategy information, and other important forecasting information, can be found in the Target Product Profile (TPP) and the Integrated Product Development Plan (IPDP). The information gathered from these documents should include, at a minimum, the data highlighted in Table 6.

Table 6: Potential Sources of Drug Candidate Information

Target Product Profile	Integrated Product Development Plan
• Indication • Target patient population • Presentation/formulation • Route of administration • Dosing schedule • Efficacy • Storage requirements	• Current product candidate status • Development phase start date and duration • Estimated date of prequalification

The target patient population cohort will be specific to an age group and may be gender-specific or target a particular sub-population. The target patient population will most often be the suspected or confirmed incident cases of the disease[10]. Once defined, incident cases can be sourced from the following reference data:

- Institute of Health Metrics and Evaluation (IHME) Global Burden of Disease estimates
- World Health Organization (WHO) disease burden estimates
- Other data source, as appropriate (e.g., UNAIDS, World Malaria Report, published literature)

MULTIPLE DRUG TREATMENT REGIMEN DEMAND FORECASTING

Although this document provides guidance on potential demand for a drug or drug combination product, it is important to recognize that potential demand could also be forecasted for a treatment regimen involving multiple drugs. Unlike vaccines, countries often use multiple drugs or drug regimens to treat a specific disease or condition because of the nuances across drug treatment formulations, regimens, effectiveness, and price. Alternative drugs or drug regimens are also helpful for combating drug resistance. For these reasons, it may be important to assess the demand for multiple drugs or drug treatment regimens targeting the same disease and population in a given country (e.g., multiple drug treatment strategies such as [2HRZE/4$(HR)_3$] or [2$(HRZE)_3$/4$(HR)_3$] can be used to treat HIV-negative patients with drug-sensitive pulmonary TB).

In these cases, the forecaster would need to assess a market share for each drug treatment strategy for each in-scope country. If new drug treatment strategies become available, the forecaster would need to determine whether a country would introduce the new strategy into their current treatment portfolio or not, and if so, adjust the market share accordingly.

POTENTIAL DRUG TREATMENT DEMAND FORECASTING METHODOLOGY

The methodology presented in this document is focused on the potential demand for a single drug or drug combination delivered via a specified treatment strategy. The potential demand forecast will be developed through a series of calculations. Each calculation requires a set of key input assumptions that should be clearly documented and transparent to those interested in the demand forecast. Table 7 identifies the calculation components and the key inputs required for each calculation.

[10] Incidence is used to avoid double-treating prevalent cases when the disease has a long duration, generally spanning more than a year.

Table 7: Drug Treatment Calculation Components and Input Requirements

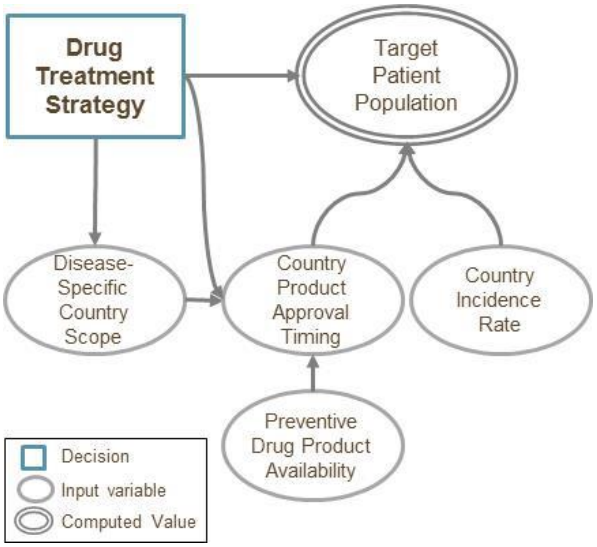
Calculation Component	Input Requirements
Target Patient Population(s)	• Disease-specific country scope • Drug product availability • Country product approval timing • Country incidence rate
Treated Patient Population	• Percent of population with access to appropriate diagnosis and treatment • Peak strategy share • Time to peak strategy share
Number of Fully and Partially Treated Patients	• Percent of patients who fully adhere
Demand in Doses	• Doses per fully treated subject • Percent of regimen completed per partially treated subject • Percent of doses not taken, but acquired, per partially treated subject
Doses Required to Cover Wastage	• Wastage (%)
Doses Required for Buffer Stock	• Buffer stock (%)

This document uses simplified "influence diagrams" to provide a step-by-step potential demand forecasting guide. Each section will highlight a piece of the overall influence diagram to help guide the reader through a section at a time. The complete influence diagram will be provided at the end of the drug intervention chapter. Within all influence diagrams, the single lined bubbles represent the input variables that must be assessed in order to develop the potential drug demand forecast. Double-lined bubbles represent calculations (e.g., adding or multiplying two or more input variables).

Target Patient Population Forecast

Figure 13 represents the input variables required to forecast the target patient population over time. Four input variables are required to forecast the target patient population for a specific drug treatment strategy.

Figure 13: Target Patient Population Forecast



Disease-Specific Country Scope

The disease-specific country scope defines which countries should be included in the potential demand forecast. The country scope should be determined based on disease burden. The country scope may include all countries if the disease is global in nature (e.g., diarrhea) or a specific set of countries if the disease is regionally focused (e.g., malaria, hookworm). Many disease burden sources will identify the highly endemic countries for a given disease, so disease-specific country scope assumptions are not typically considered highly uncertain or difficult to make.

Drug Product Availability

If a country is expected to eventually introduce a drug or drug combination product, the earliest possible introduction date will be dependent on the availability of the product. A drug product is considered available when it has been licensed by a National Regulatory Authority (NRA) for the first time. If there are multiple drug products included in the treatment strategy, then drug product availability would be the year in which the last of the drugs in the combination is licensed. This first licensure does not imply that any country can introduce at that time given a country must satisfy its own regulatory requirements before introduction can occur.

Because drug product availability is dependent on the successful execution and timing of the product development plan and the successful completion of supporting activities (e.g., manufacturing scale-up), the timing for product availability can be highly uncertain. Comparing development plan timing assumptions to appropriate benchmarks or similar plans that have already been completed can sometimes help mitigate some of the assessment uncertainty. Accounting for uncertainty by assessing timing ranges for each activity to enable a probability-weighted timing assessment can also help capture the uncertainty associated with product availability.

Country Product Approval Timing

Countries typically require national licensure to introduce drugs into the public and private sector and each country has its own licensure requirements and processes. For some countries, and donors, WHO prequalification might also be required.

Licensure of a new product within a country is dependent on the country and the supplier. A country must be motivated to license a particular product for national use and a supplier must be willing to support the licensure process for that particular country. Although suppliers are highly motivated to maximize the number of countries licensing their products, the timing for obtaining each of those regulatory approvals is driven by the supplier's own priorities. When a country knows its disease burden is high, is motivated to reduce that burden, and believes a specific product can be instrumental in addressing that burden, a country can proactively engage with suppliers to accelerate initiation of the approval process.

Because drug product availability can be uncertain, country product approval timing methodologies typically define approval timing in terms of years from initial drug product availability. By taking this approach, the approval timing will shift appropriately if the product availability assessment is modified.

Table 8 identifies some of the more common factors that may influence country product approval timing.

Table 8: Common Factors that Influence Drug Treatment Approval Timing

Country Drug Approval Timing Factors
• Disease burden • National disease policy • Safety and efficacy • Unmet needs

Disease Burden

Disease burden can be a major influencer of country product approval. The greater the burden, the more likely a country will license a product if there are no other confounding issues. The greater the disease impact, the earlier a country is likely to approve a new product, although there are always exceptions. Country-specific disease burden data can be obtained from a variety of sources (e.g., WHO, IHME). Although each source has its believers and detractors, using the same source whenever possible will mitigate differences based on disease burden methodologies alone.

Not all countries that experience disease burden will choose to license or otherwise "approve" a specific new drug. Different factors may influence whether a country will actually approve a new drug product for national use. For example, countries may have concerns about the efficacy or safety of the drug in its own populations or relative to other available treatment strategies.

National Disease Policy

Many countries have national disease policies in place that state the country's control, elimination, or eradication goals. These policies can be used to guide product approval and timing assessments. If a country does not have a national policy in place for a given disease, then approval of a drug might not be considered as high a priority. On the other hand, if a country has an elimination or eradication strategy in place, the country may be highly motivated to rapidly approve a new drug treatment strategy if perceived to be helpful to their disease policy goal.

Safety and Efficacy

Country licensure will be more likely and earlier rather than later if the drug treatment strategy has demonstrated equivalent or superior safety and efficacy relative to the existing standard of care. Safety and efficacy data may come from clinical trial outcomes, demonstration studies, or evidence of post-introduction impact from other countries.

Unmet Needs

Country approval of a new drug treatment strategy may also be affected by the degree to which the new product is addressing an unmet need. If the specific disease does not have an effective treatment or prevention strategy, the new product may be more likely to be prioritized for licensure.

Country Product Approval Information Sources

Potential sources of country product approval timing include:

- PDP demand forecasts (e.g., TB Alliance, MMV)
- Other forecasts (e.g., UNITAID, CHAI, suppliers)

Country Incidence Rate

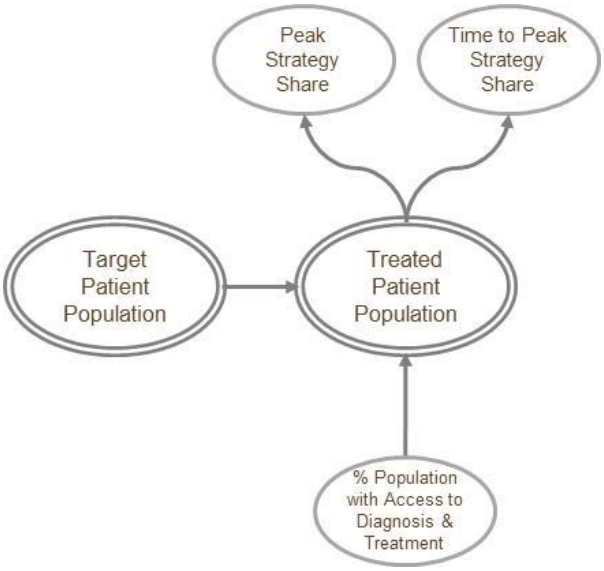
For a given country expected to approve a new drug treatment strategy, the target patient population will depend on the disease incidence rate for that country. The incidence rate is a person's probability of being diagnosed with a disease during a given period of time. The incidence rate is usually specified as newly diagnosed cases per 100,000 people. When determining the incidence rate, care must be taken to ensure the incidence rate is for the appropriate target patient population (e.g., children under 5yo; women of child-bearing age). If the incidence rate is not available for demographic-driven cohorts, the forecaster will need to assess an incidence rate given knowledge of the disease distribution by age, gender, etc. Information on the distribution of disease burden in a population can often be found through literature review.

The multiplication of the target patient population by the incidence rate, for a given country, will result in the target patient population.

Treated Patient Population Forecast

Figure 14 represents the input variables required to forecast the treated patient population over time. Three input variables are required to forecast the treated patient population for a specific drug treatment strategy.

Figure 14: Treated Patient Population Forecast



Percent Population with Access to Diagnosis and Treatment

An assessment of the percent of the target patient population that will have access to a health care facility with the required diagnostic and treatment options will need to be completed for all drug treatment strategies. While access to treatment has improved, not all subjects will have access to a diagnosis and treatment-ready health care facility. This assessment will determine what percentage of the target patient population will actually be able to receive treatment.

Many diseases can be diagnosed clinically while some require a diagnostic test. This variable assumes that once a patient is diagnosed, the drug treatment of interest will be available in the same facility. Therefore, if a patient has access to a facility or healthcare worker capable of diagnosing a specific disease or condition, then it is assumed that patient will be treated by some drug treatment strategy.

Although a positive clinical diagnosis may be a misdiagnosis, the treatment of that misdiagnosed case does require drug product, and therefore, is included in the potential demand forecast. If the demand forecast will later be used in a health impact analysis, consideration should be given to the percent of treated patients misdiagnosed so that the health impact is not overstated.

Although typically difficult to find, patient access information can be found in literature. Historically reported patient treatment data can also be used as a proxy for access and diagnosis. If information cannot be found, it is best to provide a broad range for the "percent of population with access" to account for the uncertainty.

Table 9 identifies several treatment coverage information sources for the top three global infectious diseases.

Table 9: Patient Treatment Information Sources

Disease	Treatment Coverage Example	Source
HIV	Estimated antiretroviral therapy coverage • Percentage of adults and children currently receiving antiretroviral therapy among all adults and children living with HIV	UNAIDS Global Report
Malaria	• % any antimalarial coverage • % ACT coverage	World Malaria Report
Tuberculosis	• Number of laboratory-confirmed TB patients who started treatment , and • Number of non-laboratory-confirmed TB patients who started treatment	WHO's Global TB Database

Peak Strategy Share

The potential demand forecasting methodology accounts for the fact that multiple drug products and treatment strategies can be used concurrently for a particular disease and target population cohort in a given country. There may be a preferred standard of care (SOC) that represents the most effective or the most commonly used treatment strategy. A new drug product entering the market would most likely compete for share with the SOC, other in-market products, or products currently in development that enter the market at a later date.

When only one treatment strategy is available or used in a country, then one would assume the potential demand would be for that particular product. If a country is expected to have more than one drug treatment strategy available, then market share for the drug product of interest would need to be assessed for each in-scope country.

Table 10 identifies several of the more common factors that will influence peak drug product strategy share.

Table 10: Common Factors that influence Peak Drug Treatment Strategy Share

Peak Drug Treatment Strategy Share Factors
• Treatment price • Treatment efficacy • Treatment side effects • Treatment regimen • Local supply • Cultural preferences/norms

Treatment Price

The expected price (per dose or treatment) of a drug treatment strategy will influence market share. A higher priced product may not be preferred unless it has demonstrated or perceived benefits to warrant selection over another less expensive product. As more competitors enter the market, price will likely be a lever for maintaining or gaining market share. For example, an in-market product may decrease its price to stave off the competition. Prices also change over time, either due to competitive market dynamics or through natural price maturation as suppliers lower prices once their product development costs have been recouped.

Treatment Efficacy

The relative efficacy or effectiveness of each drug treatment strategy will also influence market share. Drug treatment strategies with higher expected effectiveness are typically more attractive to medical professionals and patients unless the product price is deemed prohibitive.

Treatment Side Effects

The safety profile of the treatment regimen will affect market share if it differs materially from the safety profile of competing regimens. Products with fewer side effects and a better safety profile will generally be preferred over those with more side effects. The number and severity of side effects for products included in the overall treatment strategy should be assessed and compared to competing product strategies when determining side effect impact on market share.

Treatment Regimen

The complexity of each regimen, in terms of the overall treatment duration and "pill burden," will also influence medical provider and patient preference, and thus market share. For example, a daily single dose treatment will likely be valued over a daily three dose treatment.

Local Supply

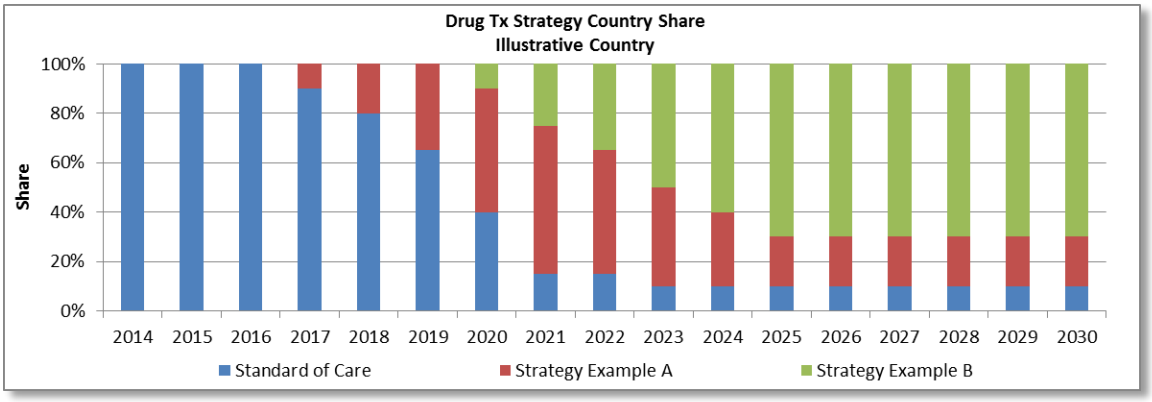
Some countries prefer, or even require, that products be manufactured locally versus imported. Understanding a country's policies on supply origination will be helpful to assessing market share for any given country.

Cultural Preferences/Norms

There may also be physician or patient preferences or cultural norms that affect how various treatment strategies will be used. Research into physician and patient treatment preferences will be particularly important for informing peak strategy share. This type of research is increasingly available through social marketing firms in developing countries.

Figure 15 provides an illustrative example of a market share forecast for three drug treatment strategies available within the same country. The SOC realizes a 100% share of the treated patient population until a new drug treatment (strategy A) is introduced in 2017. Share changes further when another new product is introduced in 2020. The decision to prioritize one product over another will depend on which product holds the most desired product characteristics, as described above.

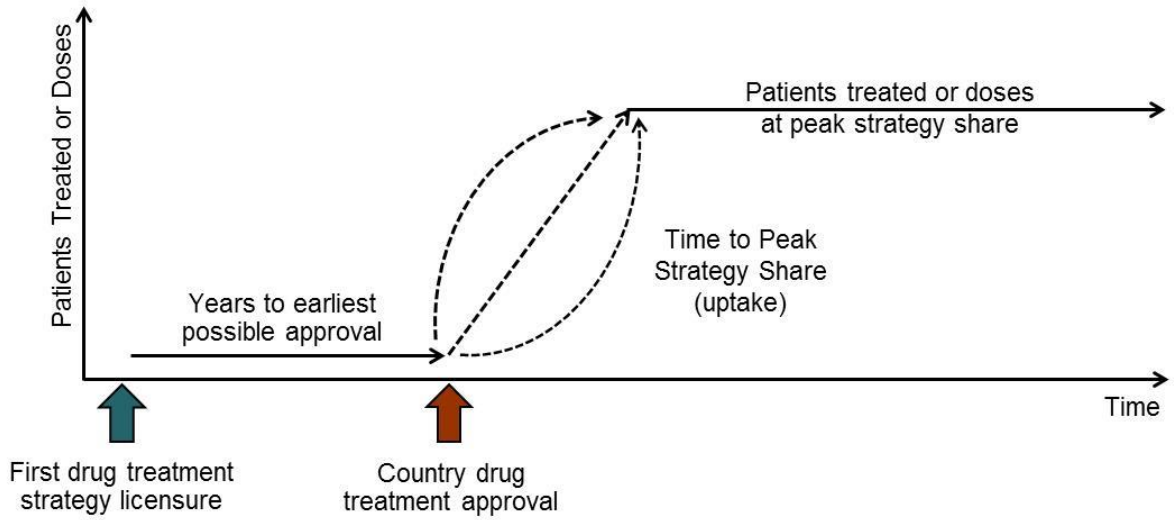
Figure 15: Illustrative Drug Treatment Strategy Share Example



Time to Peak Strategy Share

The final input required to forecast Treated Patient Population is time to peak strategy share. Time to peak strategy share is a country-specific assessment that represents the number of years it takes to reach peak strategy share, starting from the year of country approval timing. The time to peak strategy share is influenced by product preference. If the new product is significantly more beneficial than the current SOC, time to peak market share should happen quickly. If the product provides only a small benefit or advantage over SOC, uptake to peak market share may take longer. Figure 16 illustrates the variables required to determine treated patient population.

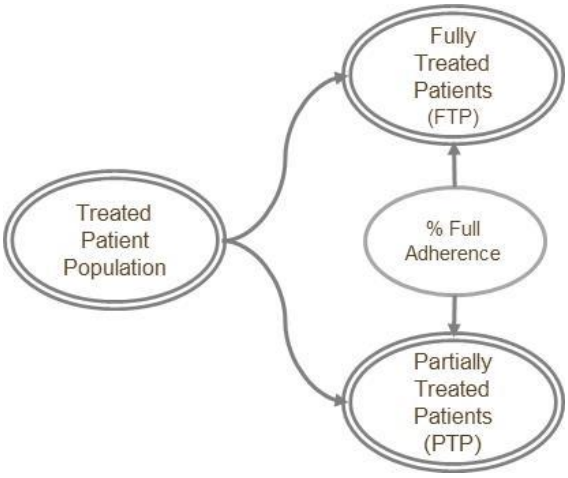
Figure 16: Treated Patient Population Forecast



Fully and Partially Treated Patients Forecast

How the treated patient population adheres to the drug treatment strategy of interest is the critical assessment for determining fully and partially treated subjects (Figure 17). Capturing the demand required to fully treat patients is critical and will represent the demand that can actually deliver a health impact. While partially treated patients are not expected to realize the full effectiveness of the treatment, the doses used on partially treated patients are important to capture for supply planning and procurement cost forecasting purposes.

Figure 17: Fully & Partially Treated Patients Forecast



Percent Full Adherence

The main variable needed to calculate fully and partially treated patients is the percentage of patients fully adhering to the drug treatment regimen.

Percent full adherence is defined as the fraction of the treated patient population that correctly follows the treatment strategy. Partially treated patients are the fraction of the treated patient population that does not complete the treatment strategy. (i.e., 1 - % Full Adherence).

Table 11 identifies several of the more common factors that will influence drug treatment strategy adherence.

Table 11: Common Factors that Influence Drug Treatment Strategy Adherence

Drug Treatment Strategy Adherence Factors
• Treatment side effects • Direct patient costs • Treatment regimen

Treatment Side Effects

The safety profile of the treatment strategy will have a significant impact on patient adherence. The types and severity of side effects should be used to assess overall adherence. A review of the product's safety profile, when used alone and in combination with other products, will inform patient adherence assessments.

Direct Patient Costs

In countries where patients pay for drug treatment out-of-pocket, it is important to consider the total price of the regimen when assessing adherence. Higher priced drug treatments that require long treatment timeframes (e.g., TB, HIV) may result in lower overall adherence compared to lower priced and shorter duration treatments.

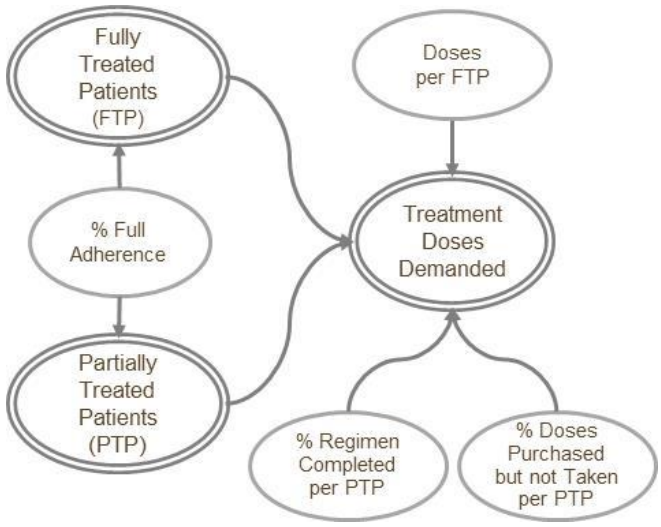
Treatment Regimen

The complexity of the regimen, in terms of overall treatment duration and "pill burden," will affect patient adherence. For example, adherence is likely to be much higher for a once daily versus three times daily treatment.

Drug Treatment Doses Demanded

The fully and partially treated patients form the basis for potential demand in number of doses. Figure 18 highlights the input variables required to forecast treatment doses demanded. For fully treated patients, the only additional variable required is the number of doses per fully treated patient.

Figure 18: Doses Demanded for Fully and Partially Treated Subjects



The number of doses per fully treated patient should be provided in the drug candidate's target product profile. If the product is already in-market, this information will be included in the product's package insert. Whenever possible, it is advisable to use product information specific for developing country settings. If developing country-relevant information cannot be obtained, drug package inserts for other markets can be used to help inform the country-specific assessment.

For partially treated patients, the "percent of regimen completed" and "percent doses purchased, but not taken" will need to be assessed. The doses purchased, but not taken variable accounts for the fact that doses may be purchased but not actually used. The percentage not taken will be influenced by the treatment complexity and duration. For example, if a drug regimen requires daily dosing for 4 months, it will important to understand how the drug is packaged and purchased. If purchased as a week's supply, there is less chance of doses not taken, but a greater chance of new purchases not being made. If purchased as a three-month supply, there is a greater chance of significant doses not being used.

Doses Required to Cover Wastage

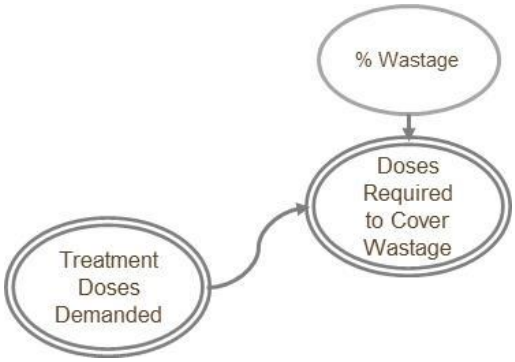
Drug treatment product wastage can be significant. Therefore, it is important to account for wastage in the final potential demand forecast. Wastage is typically defined as a percentage of the doses demanded for treatment. Figure 19 highlights the relationship between wastage-related input and output variables.

The wastage rate is the percentage of demanded doses (i.e., procured doses) that will be unavailable for treatment use because of loss, damage, theft, or inadequate storage. The doses required to cover wastage is equal to the number of doses demanded divided by 1 minus the percent wastage.

Drug wastage rates depend on multiple criteria, including product expiry dates, transportation methods, cold-chain storage requirements, etc. Estimates for drug wastage rates can often be found in published literature[11] or global health organization reports.

[11] For example, an estimate of 25% drug wastage was used when calculating the costs of child and antenatal malaria chemoprophylaxis. Source: Goodman C., Coleman P. & MA. Economic Analysis of Malaria Control in Sub-Saharan Africa. Geneva: Global Forum for Health Research. 2000. http://www.givewell.org/files/DWDA 2009/Analysis/Economic Analysis of Malaria Control in Sub-Saharan Africa.pdf.

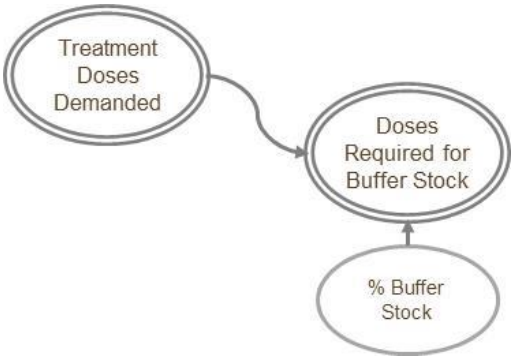
Figure 19: Doses Required to Cover Wastage



Doses Required for Buffer Stock

Buffer stock is additional drug stock kept at the country level to help avoid product stock-outs. Buffer stock provides countries with surplus doses should they be needed to meet faster than expected demand or to mitigate the impact of potential future supply shortages. Figure 20 highlights the relationship between buffer stock-related input and output variables.

Figure 20: Doses Required for Buffer Stock



Country specific information about the amount of buffer stock procured is often difficult to find. Buffer stock amounts and rates of replenishment are generally set by country managers at the programmatic level, and take into account the storage capacity and shelf life of the product. For forecasting purposes, buffer stock defaults can be defined for drug treatment products or classes of similar products.

As a general guideline, USAID recommends a buffer stock equal to at least half of the demand procured in a defined period, generally quarterly.[12] If demand is highly uncertain, buffer stock can be increased to account for unexpected demand. Buffer stock can be purchased all at once or over a specified procurement period.

POTENTIAL DRUG TREATMENT DEMAND FORECASTING METHODOLOGY SUMMARY

The complete methodology for determining potential drug treatment demand for a single drug or drug combination product is summarized in Figure 21.

Figure 21: Potential Drug Treatment Demand Methodology

[12] USAID Deliver. The Logistics Handbook: A Practical Guide for the Supply Chain Management of Health Commodities., 2011.

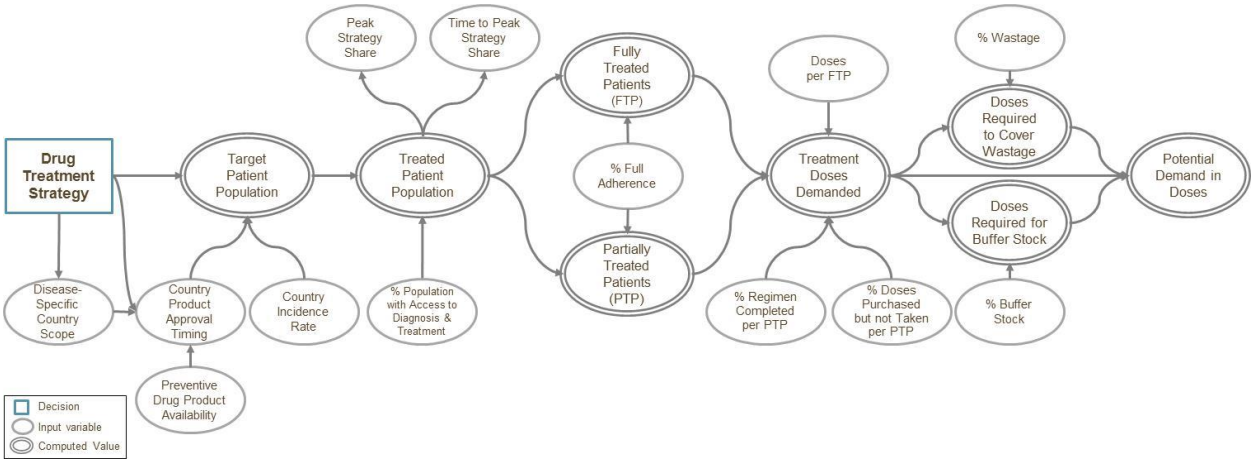
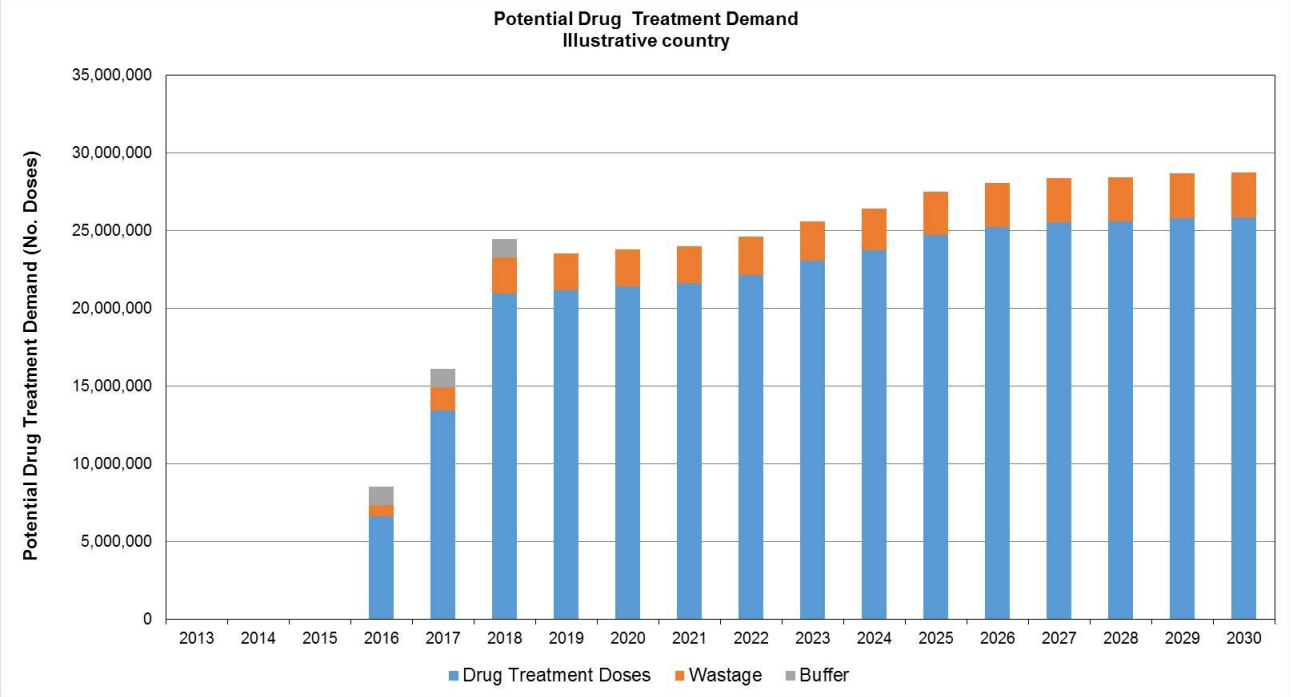


Figure 22 provides an example of the potential doses demanded forecast for a drug product in an illustrative country. In this example, drug treatment uptake increases to peak demand levels in that country in a linear fashion over three years; 33% of the required buffer stock for that country is purchased in each of the first three years; and wastage accounts for the remaining doses the country will need to procure.

Figure 22: Potential Drug Treatment Demand Example



Prevention Drug Treatments

PREVENTION DRUG TREATMENT STRATEGY

Prevention drug treatments are biomedical interventions used for the prevention of a symptom, condition, disease, or combination of diseases. Prevention drug treatment examples include pre-exposure prophylaxis (PrEP), malaria prophylactic treatment, and oral contraceptives. The methodology for forecasting potential demand for prevention drug treatments is very similar to the drug treatment strategy demand forecasting methodology.

To forecast potential demand, every prevention drug candidate or prevention drug candidate in combination with other products will need a clearly defined strategy that will inform how and to whom the products will be delivered in the field. A prevention drug treatment strategy is defined by its prevention drug treatment regimen (how to protect), the associated target population cohort (who to protect), and the specific condition, disease, or disease combination (what to protect against). Each country's demand for a candidate-specific prevention strategy contributes to the overall potential demand forecast.

When defining a prevention drug treatment strategy, four key elements need to be specified. Figure 23 describes these four elements.

Figure 23: Prevention Drug Treatment Strategy Elements

Prevention Drug Treatment Strategy — Defined by:

Strategy Element	Description	Examples
Target Disease or Condition	Disease , disease combination, or condition targeted by the product candidate	• Pregnancy • HIV
Target Cohort Age & Gender	Age and gender cohort that is intended to receive the product once it becomes available	• Women of Child Bearing Age • 14 to 59 year old males
Population Subset	Subset of the target cohort based on demographic or user defined characteristics	• HIV- • Commercial sex workers
Prevention Drug Treatment Regimen	The dosing and treatment schedule required to achieve full product effectiveness	• Contraceptive implant every three months • 1 tablet twice daily for one day

Through the specification of these four elements, any prevention drug treatment strategy can be defined.

Prevention Drug Treatment Strategy Example

- Sulfadoxine / pryimethamine administered to pregnant women at each antenatal care visit starting in the 2nd trimester and up to time of delivery (1500mg/75mg SP) to prevent *P. falciparum* malaria during pregnancy

Prevention drug treatment strategy information, and other important forecasting information, can be found in the Target Product Profile (TPP) and the Integrated Product Development Plan (IPDP). The information gathered from these documents should include, at a minimum, the data highlighted in Table 12.

Table 12: Potential Sources of Prevention Drug treatment Candidate Information

Target Product Profile	Integrated Product Development Plan
• Indication • Target population (e.g., age, gender) • Presentation/formulation • Route of administration • Dosing schedule • Efficacy • Storage requirements	• Current product candidate status • Development phase start date and duration • Estimated date of prequalification

The target population cohort will be specific to an age group and may be gender-specific or target a particular sub-population. The target population will most often be the population most at risk for contracting the condition or disease. Once defined, the target population data by country can typically be sourced from the following reference data:

- UN World Population Prospects (revised annually)
- World Bank, HNP Database Population Projections (revised annually)
- Other data source, as appropriate (e.g., subnational population data, % of population at risk)

POTENTIAL PREVENTION DRUG DEMAND FORECASTING METHODOLOGY

The methodology presented in this document is focused on the potential demand for a single prevention drug treatment or combination prevention drug treatment delivered via a specified strategy. The potential demand forecast will be developed through a series of calculations. Each calculation requires a set of key input assumptions that should be clearly documented and transparent to those interested in the demand forecast. Table 13 identifies the calculation components and the key inputs required for each calculation.

Table 13: Prevention Drug Treatment Calculation Components and Input Requirements

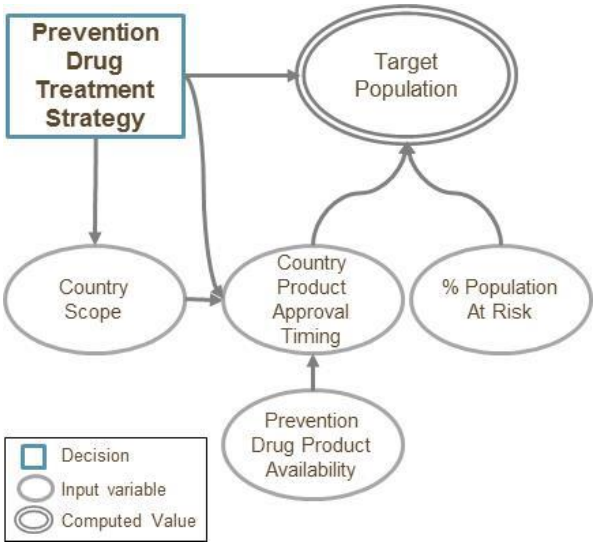
Calculation Component	Input Requirements
Target Population(s)	• Country scope • Prevention drug product availability • Country product approval timing • Percent population at risk
Protected Population	• Percent of population with access to prevention drug treatments • Peak strategy share • Time to peak strategy share
Number of Fully and Partially Protected Subjects	• Percent of subjects who fully adhere
Demand in Doses	• Doses per fully protected subject • Percent of regimen completed per partially protected subject • Percent of doses not taken, but acquired, per partially protected subject
Doses Required to Cover Wastage	• Wastage (%)
Doses Required for Buffer Stock	• Buffer stock (%)

This document uses simplified “influence diagrams” to provide a step-by-step potential demand forecasting guide. Each section will highlight a piece of the overall influence diagram to help guide the reader through a section at a time. The complete influence diagram will be provided at the end of the drug intervention chapter. Within all influence diagrams, the single lined bubbles represent the input variables that must be assessed in order to develop the potential drug demand forecast. Double-lined bubbles represent calculations (e.g., adding or multiplying two or more input variables).

Target Population Forecast

Figure 24 represents the input variables required to forecast the target population over time. Four input variables are required to forecast the target population for a specific prevention drug treatment strategy.

Figure 24: Prevention Drug Treatment Target Population Forecast



Country Scope

The country scope defines which countries should be included in the potential demand forecast. The country scope should be determined based on condition prevalence or disease burden. The country scope may include all countries if the condition or disease is global in nature (e.g., pregnancy) or a specific set of countries if the condition or disease is regionally focused (e.g., malaria).

Prevention Drug Product Availability

If a country is expected to eventually introduce a prevention drug treatment or prevention drug treatment combination product, the earliest possible introduction date will be dependent on the availability of the product. A prevention drug product is considered available when it has been licensed by a National Regulatory Authority (NRA) for the first time. If there are multiple prevention drug products included in the prevention strategy, then prevention drug product availability would be the year in which the last of the drugs in the combination is licensed. This first licensure does not imply that any country can introduce at that time given a country must satisfy its own regulatory requirements before introduction can occur.

Because prevention drug product availability is dependent on the successful execution and timing of the product development plan and the successful completion of supporting activities (e.g., manufacturing scale-up), the timing for product availability can be highly uncertain. Comparing development plan timing assumptions to appropriate benchmarks or similar plans that have already been completed can sometimes help mitigate some of the assessment uncertainty. Accounting for uncertainty by assessing timing ranges for each activity to enable a probability-weighted timing assessment can also help capture the uncertainty associated with product availability.

Country Product Approval Timing

Countries typically require national licensure to introduce prevention drug treatments into the public and private sector and each country has its own licensure requirements and processes. For some countries, and donors, WHO prequalification might also be required.

Licensure of a new product within a country is dependent on the country and the supplier. A country must be motivated to license a particular product for national use and a supplier must be willing to support the licensure process for that particular country. Although suppliers are highly motivated to maximize the number of countries licensing their products, the timing for obtaining each of those regulatory approvals is driven by the supplier's own priorities. When a country knows its disease burden is high, is motivated to prevent or reduce that burden, and

believes a specific product can be instrumental in addressing that burden, a country can proactively engage with suppliers to accelerate initiation of the approval process.

Because prevention drug treatment product availability can be uncertain, country product approval timing methodologies typically define approval timing in terms of years from initial prevention drug treatment availability. By taking this approach, the approval timing will shift appropriately if the product availability assessment is modified. Table 14 identifies some of the more common factors that may influence country product approval timing.

Table 14: Common Factors that Influence Prevention Drug Treatment Approval Timing

Country Prevention Drug Treatment Approval Timing Factors
• Disease burden • At-risk population • National disease policy • Safety and efficacy • Unmet needs

Disease Burden

Disease burden can be a major influencer of country product approval. The greater the burden, the more likely a country will license a product if there are no other confounding issues. The greater the disease impact, the earlier a country is likely to approve a new product, although there are always exceptions. Country-specific disease burden data can be obtained from a variety of sources (e.g., WHO, IHME). Although each source has its believers and detractors, using the same source whenever possible will mitigate differences based on disease burden methodologies alone.

Not all countries that experience disease burden will choose to license or otherwise "approve" a specific new prevention drug treatment. Different factors may influence whether a country will actually approve a new product for national use. For example, countries may have concerns about the efficacy or safety of the prevention drug treatment in its own populations or relative to other available prevention strategies.

At-Risk Population

Given prevention drug treatments target populations not currently experiencing a specific condition or disease, how much of the target population is at risk for contracting a particular condition or disease could have a significant impact on product approval timing. A country with high disease burden and a large percentage of the population at risk for contracting the disease would be more likely to approve the product quickly.

National Disease Policy

Many countries have national disease policies in place that state the country's control, elimination, or eradication goals. These policies can be used to guide product approval and timing assessments. If a country does not have a national policy in place for a given disease, then approval of a prevention drug treatment might not be considered as high a priority. On the other hand, if a country has an elimination or eradication strategy in place, the country may be highly motivated to rapidly approve a new prevention drug treatment strategy if perceived to be helpful to their disease policy goal.

Safety and Efficacy

Country licensure will be more likely and earlier rather than later if the prevention drug treatment strategy has demonstrated better safety and efficacy relative to existing prevention strategies. Safety and efficacy data may come from clinical trial outcomes, demonstration studies, or evidence of post-introduction impact from other countries.

Unmet Needs

Country approval of a new prevention drug treatment strategy may also be affected by the degree to which the new product is addressing an unmet need. If the specific disease does not have an effective treatment or prevention strategy, the new product may be more likely to be prioritized for licensure.

Country Product Approval Information Sources

Potential sources of country product approval timing include:

- PDP demand forecasts (e.g., TB Alliance, MMV)
- Other forecasts (e.g., UNITAID, CHAI, suppliers)

Percent Population at Risk

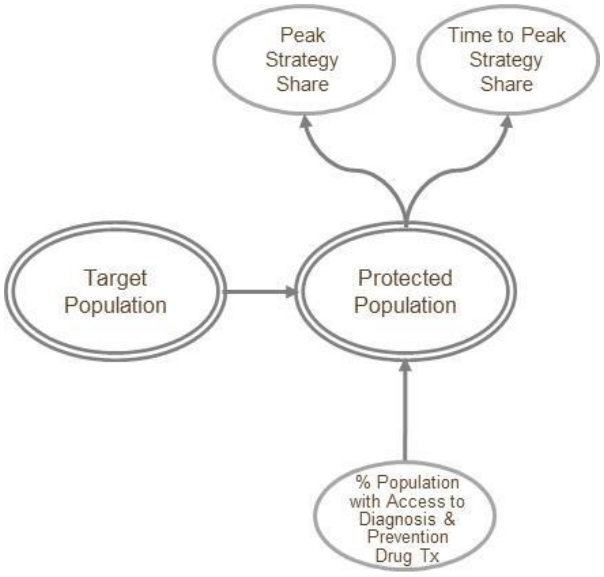
Given prevention drug treatments target populations not currently experiencing a specific condition or disease, the percent of the target population at risk for contracting a particular condition or disease will greatly influence market size. For example, if the prevention drug treatment strategy is to stop the transmission of HIV in sexually active females, the population at risk would include all females across a very broad age range.

The multiplication of the population cohort and the percent of the population cohort at risk, for a given country, will result in the target population.

Protected Population Forecast

Figure 25 represents the input variables required to forecast the protected population over time. Three input variables are required to forecast the protected population for a specific prevention drug treatment strategy.

Figure 25 Protected Population Forecast



Percent Population with Access to Diagnosis and Prevention Drug Treatment

An assessment of the percent of the target population that will have access to a health care facility with the required diagnostic services and prevention drug treatment will need to be completed for all prevention drug treatment strategies. While access to prevention interventions has improved, not all subjects will have access to a diagnosis and treatment-ready health care.

Many diseases can be diagnosed clinically while others require a diagnostic test. This variable assumes once a patient is diagnosed, the drug treatment of interest will be available in the same facility.

This assessment will determine what percentage of the target population will be able to receive a diagnosis and the prevention drug treatment.

Although typically difficult to find, access information can be found in literature. Historically reported treatment data can also be used as a proxy for access to prevention treatments. If information cannot be found, it is best to provide a broad range for the "percent of population with access" to account for the uncertainty.

Peak Strategy Share

The potential demand forecasting methodology accounts for the fact multiple prevention drug treatment products can be used concurrently for a particular condition or disease in a given country. There may be a preferred standard of care (SOC) that represents the most effective or the most commonly used prevention drug treatment strategy. A new prevention drug treatment product entering the market would most likely compete for share with the SOC, other in-market products, or products currently in development that enter the market at a later date.

When only one prevention drug treatment strategy is available or used in a country, then one would assume the potential demand would be for that particular product. If a country is expected to have more than one prevention drug treatment strategy available, then market share for the drug product of interest would need to be assessed for each in-scope country.

Table 15 identifies several of the more common factors that will influence peak prevention drug treatment product strategy share.

Table 15: Common Factors that Influence Peak Prevention Drug Treatment Strategy Share

Peak Prevention Drug Treatment Strategy Share Factors
• Treatment price • Treatment efficacy • Treatment side effects • Treatment regimen • Local supply • Cultural preferences/norms

Treatment Price

The expected price (per dose or treatment) of a prevention drug treatment strategy will influence market share. A higher priced product may not be preferred unless it has demonstrated or perceived benefits to warrant selection over another less expensive product. As more competitors enter the market, price will likely be a lever for maintaining or gaining market share. For example, an in-market product may decrease its price to stave off the competition. Prices also change over time, either due to competitive market dynamics or through natural price maturation as suppliers lower prices once their product development costs have been recouped.

Treatment Efficacy

The relative effectiveness of each prevention drug treatment strategy will also influence market share. Prevention drug treatment strategies with higher expected effectiveness are typically more attractive unless the product price is deemed prohibitive.

Treatment Side Effects

The safety profile of the prevention drug treatment regimen will affect market share if it differs materially from the safety profile of competing regimens. Products with fewer side effects and a better safety profile will generally be preferred over those with more side effects. The number and severity of side effects for products included in the overall treatment strategy should be assessed and compared to competing product strategies when determining side effect impact on market share.

Treatment Regimen

The complexity of each regimen, in terms of the overall treatment duration and "pill burden," will also influence medical provider and patient preference, and thus market share. For example, a daily single dose treatment will likely be valued over a daily three dose treatment.

Local Supply

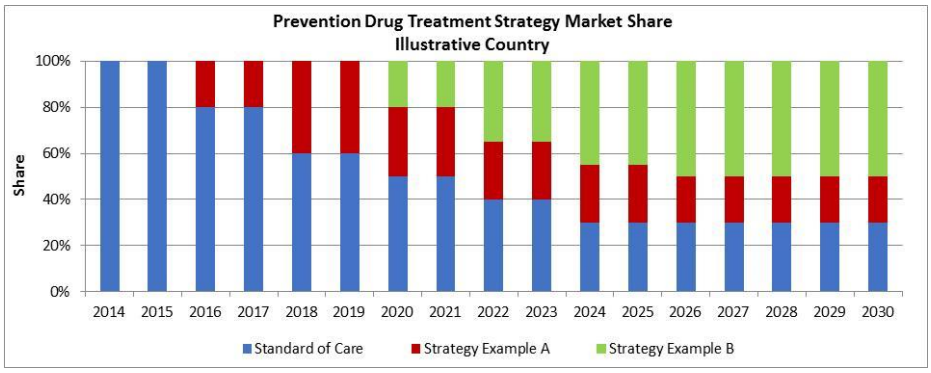
Some countries prefer, or even require, that products be manufactured locally versus imported. Understanding a country's policies on supply origination will be helpful to assessing market share.

Cultural Preferences/Norms

There may also be preferences or cultural norms that affect how various prevention drug treatment strategies will be used. Research into preferences will be particularly important for informing peak strategy share. This type of research is increasingly available through social marketing firms in developing countries

Figure 26 provides an illustrative example of a market share forecast for three prevention drug treatment strategies available within the same country. The SOC realizes a 100% share of the target population until a new prevention drug treatment (strategy A) is introduced in 2017. Share changes further when another new product is introduced in 2020. The decision to prioritize one product over another will depend on which product holds the most desired product characteristics, as described above.

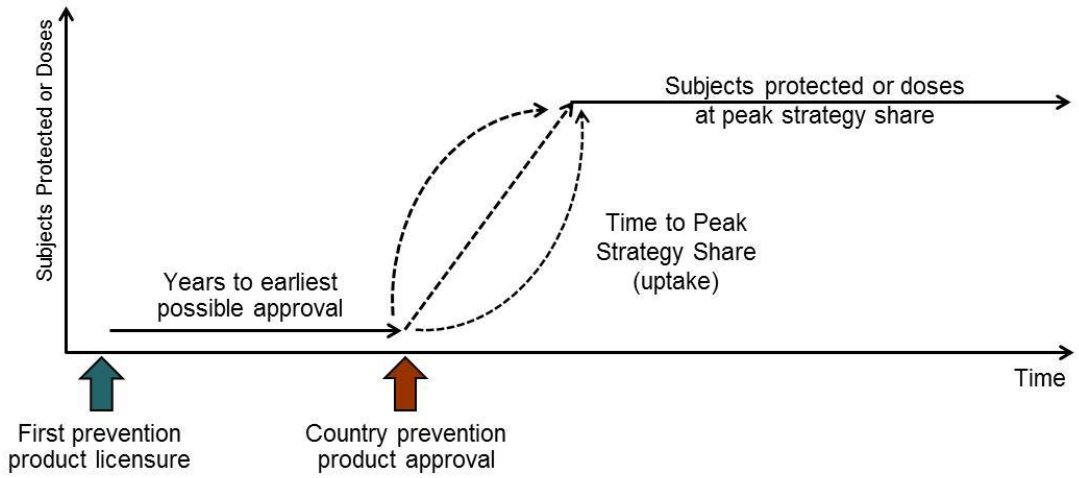
Figure 26: Illustrative Prevention Drug Treatment Strategy Share Example



Time to Peak Strategy Share

The final input required to forecast the protected population is time to peak strategy share. Time to peak strategy share is a country-specific assessment that represents the number of years it takes to reach peak strategy share, starting from the year of country approval. The time to peak strategy share is influenced by product preference. If the new product is significantly more beneficial than the current SOC, time to peak market share should happen quickly. If the product provides only a small benefit or advantage over SOC, uptake to peak market share may take longer. Figure 27 illustrates the variables required to determine protected population.

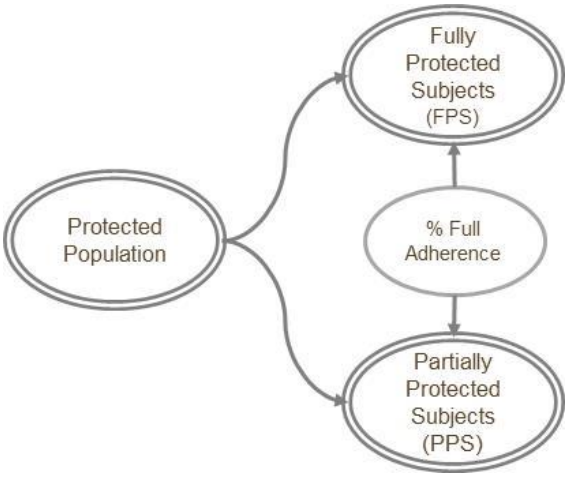
Figure 27: Protected Population Forecast



Fully and Partially Protected Subjects Forecast

How the protected population adheres to the prevention drug treatment strategy is the critical assessment for determining fully and partially protected subjects (Figure 28). Capturing the demand required to fully protect subjects is critical and will represent the demand that can actually deliver a health impact. While partially protected subjects are not expected to realize the full effectiveness of the treatment, the doses used on partially protected subjects are important to capture for supply planning and procurement cost forecasting purposes.

Figure 28: Fully & Partially Protected Subjects Forecast



Percent Full Adherence

The main variable needed to calculate fully and partially protected subjects is the percentage of subjects fully adhering to the prevention drug treatment regimen.

Percent full adherence is defined as the fraction of the protected population that correctly follows the treatment strategy. Partially protected patients are the fraction of the protected population that does not complete the treatment strategy. (i.e., 1 - % Full Adherence).

Table 16 identifies several of the more common factors that will influence prevention drug treatment strategy adherence.

Table 16: Common Factors that Influence Prevention Drug Treatment Adherence

Prevention Drug Treatment Adherence Factors
• Treatment side effects • Direct costs • Treatment regimen

Treatment Side Effects

The safety profile of the prevention drug treatment strategy will have a significant impact on adherence. The types and severity of side effects should be used to assess overall adherence. A review of the product's safety profile, when used alone and in combination with other products, will inform adherence assessments.

Direct Costs

In countries where people pay for prevention drug treatment out-of-pocket, it is important to consider the total price of the regimen when assessing adherence. Higher priced prevention drug treatments that require long treatment timeframes may result in lower overall adherence compared to lower priced and shorter duration treatments.

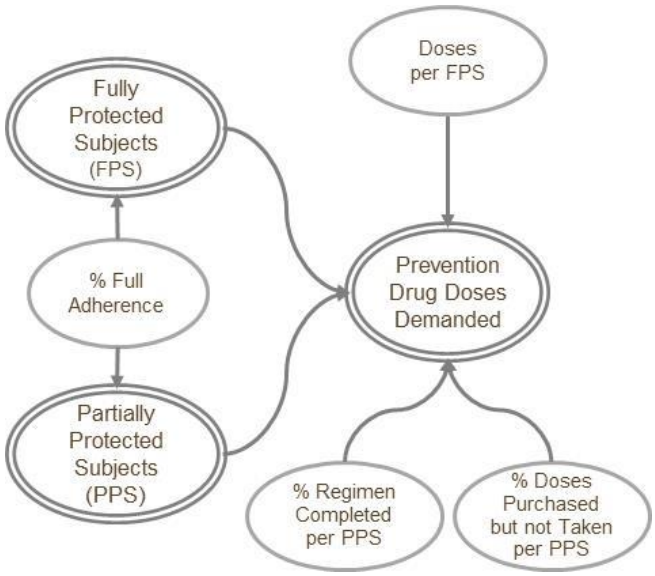
Treatment Regimen

The complexity of the regimen, in terms of the overall duration of treatment and "pill burden," will affect adherence. For example, adherence will be much higher for a once daily treatment versus a three times daily treatment.

Prevention Drug Doses Demanded

The fully and partially protected subjects form the basis for potential demand in number of doses. Figure 29 highlights the input variables required to forecast prevention drug doses demanded. For fully protected patients, the only additional variable required is the number of doses per fully protected subject.

Figure 29: Doses Demanded for Fully and Partially Protected Subjects



The number of doses per fully protected subject should be provided in the prevention drug treatment candidate's target product profile. If the product is already in-market, this information will be included in the product's package insert. Whenever possible, it is advisable to use product information specific for developing country settings. If developing country-relevant information cannot be obtained, drug package inserts for other markets can be used to help inform the country-specific assessment.

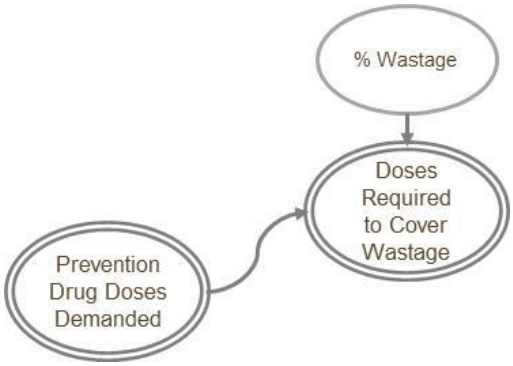
For partially protected subjects, the "percent of regimen completed" and "percent doses purchased, but not taken" will need to be assessed. The doses purchased, but not taken variable accounts for the fact that doses may be purchased but not actually used. The percentage not taken will be influenced by the regimen complexity and duration. For example, if a prevention drug treatment regimen requires daily dosing, it will important to understand how the drug is packaged and purchased. If purchased as a week's supply, there is less chance of doses not taken, but a greater chance of new purchases not being made. If purchased as a three-month supply, there is a greater chance of significant doses not being used.

Doses Required to Cover Wastage

Drug prevention product wastage can be significant. Therefore, it is important to account for wastage in the final potential demand forecast. Wastage is typically defined as a percentage of the doses demanded for prevention. Figure 30 highlights the relationship between wastage-related input and output variables.

The wastage rate is the percentage of demanded doses (i.e., procured doses) that will be unavailable for prevention purposes because of loss, damage, theft, or inadequate storage. The doses required to cover wastage is equal to the number of doses demanded divided by 1 minus the percent wastage.

Figure 30: Doses Required to Cover Wastage

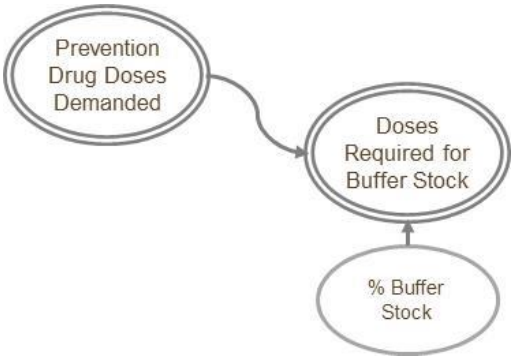


Drug wastage rates depend on multiple criteria, including product expiry dates, transportation methods, cold-chain storage requirements, etc. Estimates for drug wastage rates can often be found in published literature or global health organization reports.

Doses Required for Buffer Stock

Buffer stock is additional drug product kept at country level to help avoid stock-outs. Buffer stock provides countries with surplus doses should they be needed to meet faster than expected demand or to mitigate the impact of potential future supply shortages. Figure 31highlights the relationship between buffer stock-related input and output variables.

Figure 31: Doses Required for Buffer Stock



Country specific information about the amount of buffer stock procured is often difficult to find. Buffer stock amounts and rates of replenishment are generally set by country managers at the programmatic level, and take into account the storage capacity and shelf life of the product. For forecasting purposes, buffer stock defaults can be defined for drug treatment products or classes of similar products.

As a general guideline, USAID recommends a buffer stock equal to at least half of the demand procured in a defined period, generally quarterly.[12] If demand is highly uncertain, buffer stock can be increased to account for unexpected demand. Buffer stock can be purchased all at once or over a specified procurement period.

POTENTIAL PREVENTION DRUG TREATMENT DEMAND FORECASTING METHODOLOGY SUMMARY

The complete methodology for determining potential prevention drug treatment demand for a single prevention drug or drug combination product is summarized in Figure 32.

Figure 32: Potential Prevention Drug Treatment Demand Methodology

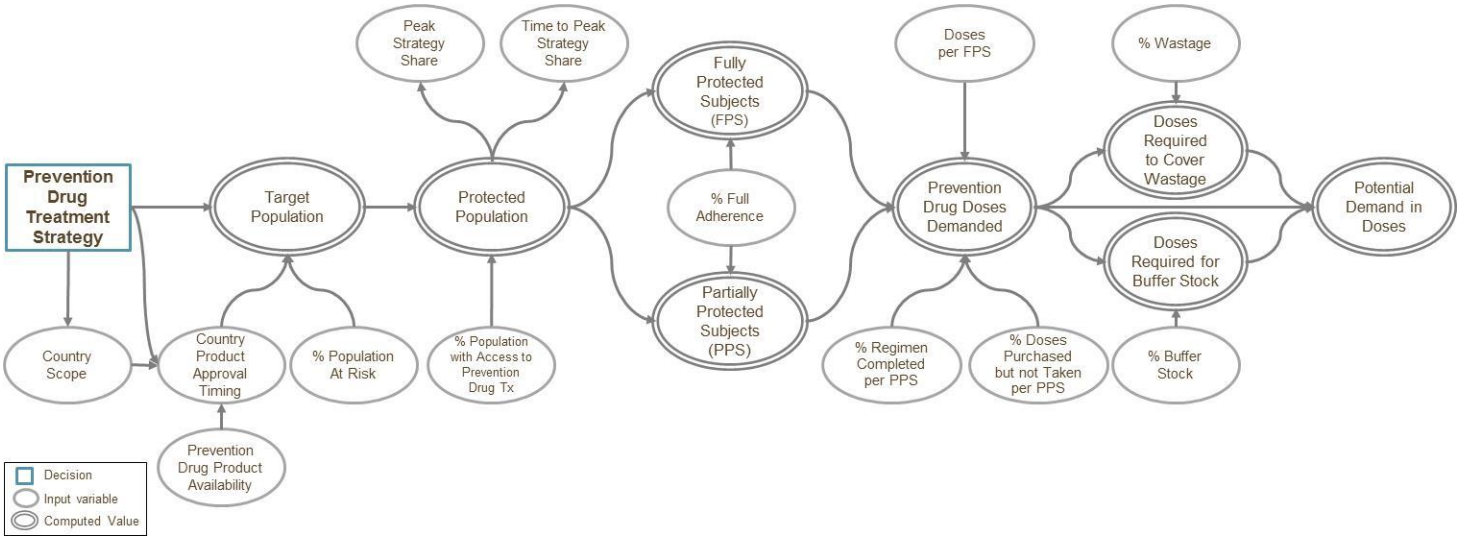
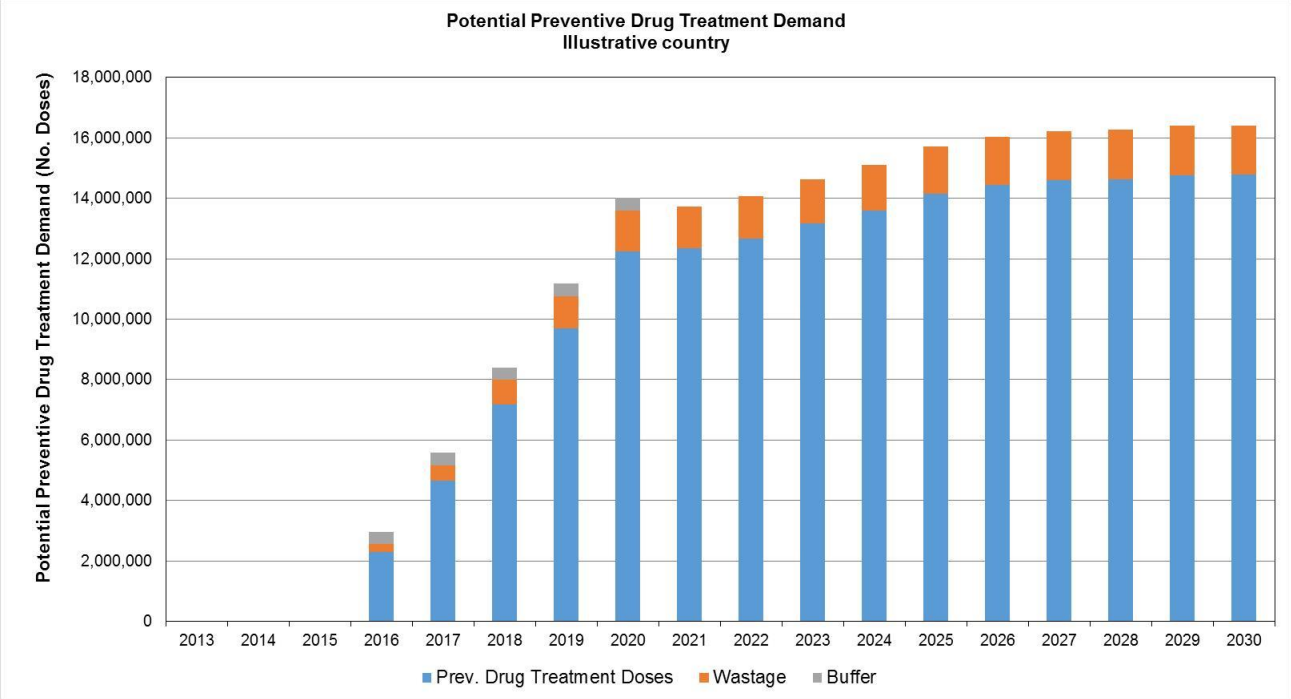


Figure 33 provides an example of the potential doses demanded forecast for a drug product in an illustrative country. In this example, drug treatment uptake increases to peak demand levels in that country in a linear fashion over three years; 33% of the required buffer stock for that country is purchased in each of the first three years; and wastage accounts for the remaining doses the country will need to procure.

Figure 33: Potential Prevention Drug Treatment Demand Example



Prevention Devices

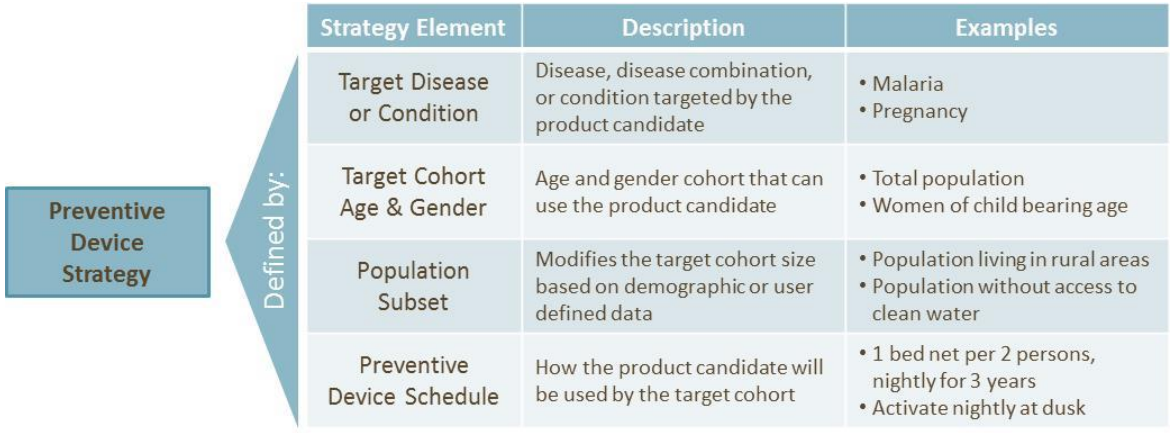
PREVENTION DEVICE PRODUCT STRATEGY

Potential demand can be forecasted for a single prevention device or multiple prevention devices targeting the same disease or condition and population. For example, if there is only one device in development for a particular disease or condition and population, the forecast will represent demand for that specific device. If there are multiple devices in development (e.g., three IUDs from three different suppliers), all targeting the same disease or condition and population with the same device use schedule, then the potential demand forecast would represent demand for the group of products (e.g., IUD demand). In this case, the demand for each individual product would not be determined.

To forecast potential demand, every prevention device candidate will need a clearly defined strategy that will inform how and to whom the products will be delivered in the field. A prevention device product strategy is defined by how it is used (how to protect), the associated target population cohort (who to protect), and the specific condition, disease, or disease combination (what to protect against). Each country's demand for a candidate-specific prevention device strategy contributes to the overall potential demand forecast.

When defining a prevention device strategy, four key elements need to be specified. Figure 34 describes these four elements.

Figure 34: Prevention Device Strategy Elements



Strategy Element	Description	Examples
Target Disease or Condition	Disease, disease combination, or condition targeted by the product candidate	• Malaria • Pregnancy
Target Cohort Age & Gender	Age and gender cohort that can use the product candidate	• Total population • Women of child bearing age
Population Subset	Modifies the target cohort size based on demographic or user defined data	• Population living in rural areas • Population without access to clean water
Preventive Device Schedule	How the product candidate will be used by the target cohort	• 1 bed net per 2 persons, nightly for 3 years • Activate nightly at dusk

Through the specification of these four elements, any prevention device strategy can be defined.

Prevention Device Strategy Example

- Single condom use per 2 person sexual act for the prevention of HIV in 15 – 69yo (sexually active subjects)
- Male circumcision device used once to non-surgically circumcise adult men (18 – 69yo) to reduce the risk of HIV infection and transmission

Prevention device strategy information, and other important forecasting information, can be found in the Target Target Product Profile (TPP) and the Integrated Product Development Plan (IPDP). The information gathered from these documents should include, at a minimum, the data highlighted in

Table 17.

Table 17: Potential Sources of Prevention Device Candidate Information

Target Product Profile	Integrated Product Development Plan
• Intended use • Target population (e.g., age, gender) • Use schedule • Storage requirements	• Current product candidate status • Development phase start date and duration • Estimated date of prequalification

The target population cohort will be specific to an age group and may be gender-specific or target a particular sub-population. The target population will most often be the population most at risk for contracting the condition or disease. Once defined, the target population data by country can typically be sourced from the following reference data:

- UN World Population Prospects (revised annually)
- World Bank, HNP Database Population Projections (revised annually)
- Other data source, as appropriate (e.g., subnational population data, % of population at risk)

POTENTIAL PREVENTION DEVICE DEMAND FORECASTING METHODOLOGY

The methodology presented in this document is focused on the potential demand for a single product or group of like products delivered via a specified strategy. The potential demand forecast will be developed through a series of calculations. Each calculation requires a set if key input assumptions that should be clearly documented and transparent to those interested in the demand forecast. Table 18 identifies the calculation components and the key inputs required for each calculation.

Table 18: Prevention Device Calculation Components and Input Requirements

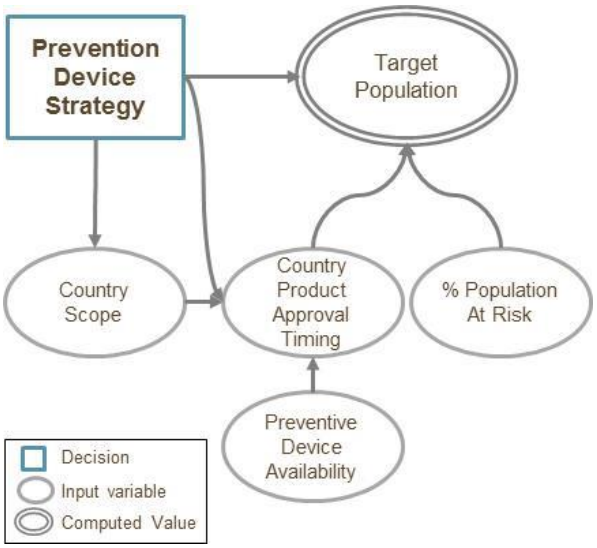
Calculation Components	Input Requirements
Target Population(s)	• Country scope • Prevention device availability • Country product approval timing • % Population at risk
Protected Population(s)	• Population with access to prevention device (%) • Peak strategy share • Time to peak strategy share
Number of Fully and Partially Protected Users	• Full adherence rate (%)
Demand in Units (# of devices)	• Average number annual uses per fully protected subject • Maximum uses per device before replacement • Maximum lifetime per device before replacement • Average number annual uses per partially protected subject • Average number devices obtained but unused per PPS
Devices Required to Cover Wastage	• Wastage rate (%)
Devices Required for Buffer Stock	• Buffer stock (%)

This document uses simplified “influence diagrams” to provide a step-by-step potential demand forecasting guide. Each section will highlight a piece of the overall influence diagram to help guide the reader through a section at a time. The complete influence diagram will be provided at the end of the drug intervention chapter. Within all influence diagrams, the single lined bubbles represent the input variables that must be assessed in order to develop the potential drug demand forecast. Double-lined bubbles represent calculations (e.g., adding or multiplying two or more input variables).

Target Patient Population Forecast

Figure 35 represents the input variables required to forecast the target population(s) over time. Four input variables are required to forecast the target population for a specific prevention device strategy.

Figure 35: Prevention Device Target Population Forecast



Country Scope

The country scope defines which countries should be included in the potential demand forecast. The country scope should be determined based on condition prevalence or disease burden. The country scope may include all countries if the condition or disease is global in nature (e.g., sexually transmitted diseases) or a specific set of countries if the condition or disease is regionally focused (e.g., malaria).

Prevention Device Availability

If a country is expected to eventually introduce a prevention device, the earliest possible introduction date will be dependent on the availability of the product. A prevention device is considered available when it has been approved by any single National Regulatory Authority (NRA) for the first time. This first approval does not imply that any country can introduce at that time given a country must satisfy its own regulatory requirements before introduction can occur.

Because the prevention device availability is dependent on the successful execution and timing of the product development plan and the successful completion of supporting activities (e.g., manufacturing scale-up), the timing for product availability can be highly uncertain. Comparing development plan timing assumptions to appropriate benchmarks or similar plans that have already been completed can sometimes help mitigate some of the assessment uncertainty. Accounting for uncertainty by assessing timing ranges for each activity to enable a probability-weighted timing assessment can also help capture the uncertainty associated with product availability.

Country Product Approval Timing

Countries typically require national licensure to introduce prevention device products into the public and private sector and each country has its own approval requirements and processes. For some countries, and donors, WHO prequalification might also be required.

Approval of a new product within a country is dependent on the country and the supplier. A country must be motivated to approve a particular product for national use and a supplier must be willing to support the approval process for that particular country. Although suppliers are highly motivated to maximize the number of countries approving their products, the timing for obtaining each of those regulatory approvals is driven by the supplier's own priorities. When a country knows its condition prevalence or disease burden is high, is motivated to prevent or

reduce that prevalence or burden, and believes a specific product can be instrumental in addressing that burden, a country can proactively engage with suppliers to accelerate initiation of the approval process.

Because prevention device product availability can be uncertain, country product approval timing methodologies typically define approval timing in terms of years from initial prevention drug treatment availability. By taking this approach, the approval timing will shift appropriately if the product availability assessment is modified. Table 19 identifies some of the more common factors that may influence product approval timing.

Table 19: Common Factors that Influence Prevention Device Approval Timing

Country Prevention Device Approval Timing Factors
• Disease burden/condition prevalence • At-risk population • National disease policy • Safety and efficacy • Unmet needs

Disease Burden or Condition Prevalence

Disease burden or condition prevalence can be major influencers of country product approval. The greater the condition prevalence or disease burden, the more likely a country will approve a product if there are no other confounding issues. The greater the condition or disease impact, the earlier a country is likely to approve a new product, although there are always exceptions. Country-specific disease burden or condition data can be obtained from a variety of sources (e.g., WHO, IHME).

Not all countries that experience the condition or disease burden will choose to license or otherwise "approve" a specific new prevention device. Different factors may influence whether a country will actually approve a new product for national use. For example, countries may have concerns about the efficacy or safety of the prevention device in its own populations or relative to other available prevention strategies.

At-Risk Population

Given prevention devices target populations not currently experiencing a specific condition or disease, how much of the target population is at risk for contracting a particular condition or disease could have a significant impact on product approval timing. A country with high disease burden or condition prevalence and a large percentage of the population at risk for contracting the disease or condition would be more likely to approve the product quickly.

National Disease Policy

Many countries have national disease policies in place that state the country's control, elimination, or eradication goals. These policies can be used to guide product approval and timing assessments. If a country does not have a national policy in place for a given disease or condition, then approval of a prevention device might not be considered as high a priority. On the other hand, if a country has an elimination or eradication strategy in place, the country may be highly motivated to rapidly approve a new prevention device if perceived to be helpful to their disease policy goal.

Safety and Efficacy

Country approval will be more likely and earlier rather than later if the prevention device has demonstrated better safety and efficacy relative to existing prevention strategies. Safety and efficacy data may come from clinical trial outcomes, demonstration studies, or evidence of post-introduction impact from other countries.

Unmet Needs

Country approval of a new prevention device may also be affected by the degree to which the new product is addressing an unmet need. If the specific disease does not have an effective treatment or prevention strategy, the new product may be more likely to be prioritized for approval.

Percent Population at Risk

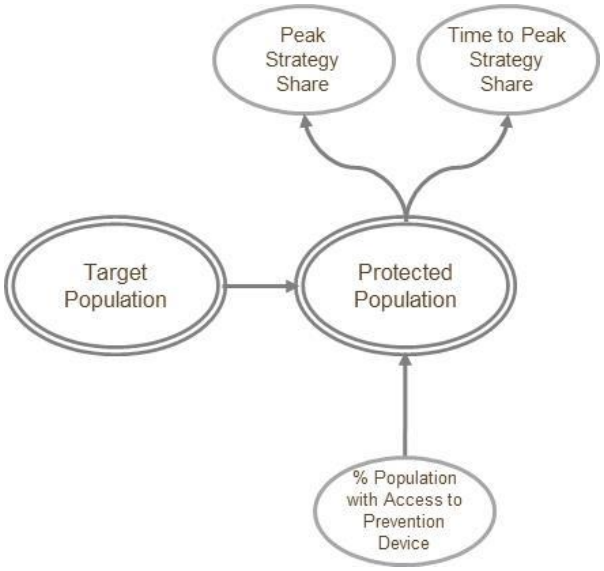
Given prevention devices target populations not currently experiencing a specific condition or disease, the percent of the target population at risk for contracting a particular condition or disease will greatly influence market size. For example, if the prevention device is to prevent malaria cases, the population at risk would include all people living in or traveling to malaria-endemic regions.

The multiplication of the population cohort and the percent of the population cohort at risk, for a given country, will result in the target population.

Protected Population Forecast

Figure 36 represents the input variables required to forecast the protected population over time. Three input variables are required to forecast the protected population for a specific prevention device strategy.

Figure 36: Prevention Device Protected Population Forecast



Percent Population with Access to Prevention Device

An assessment of the percent of the target population that will have access to the prevention device will need to be completed for all prevention device strategies. While access to such devices has improved, not all subjects will have access to these devices. Identifying the likely channels for delivering the device will provide insight on the degree of access. For example, access may be quite different if the device is to be delivered via a private pharmacy versus a community health care facility.

Peak Strategy Share

The potential demand forecasting methodology accounts for the fact multiple prevention products can be available at the same time for a particular condition or disease in a given country. There may be a preferred standard of care (SOC) that represents the most effective or the most commonly used prevention strategy. A new prevention product entering the market would most likely compete for share with the SOC, other in-market products, or products currently in development that enter the market at a later date.

When only one prevention device is available or used in a country, then one would assume the potential demand would be for that particular product. If a country is expected to have more than one prevention strategy available, then market share for the prevention device of interest would need to be assessed for each in-scope country.

Table 20 identifies several of the more common factors that will influence peak product share for a prevention device.

Table 20: Common Factors that Influence Peak Prevention Device Product Share

Peak Prevention Device Product Share Factors
• Device price • Device effectiveness • Device side effects • Device use requirements • Local supply • Cultural preferences/norms

Device Price

The expected price of the device and the price per device use will influence market share. A higher priced product may not be preferred unless it has demonstrated or perceived benefits to warrant selection over another less expensive product. As more competitors enter the market, price will likely be a lever for maintaining or gaining market share. For example, an in-market product may decrease its price to stave off the competition. Prices also change over time, either due to competitive market dynamics or through natural price maturation as suppliers lower prices once their product development costs have been recouped.

Device Effectiveness

The relative effectiveness of each prevention device strategy will also influence market share. Prevention device strategies with higher expected effectiveness are typically more attractive unless the product price is deemed prohibitive.

Device Side Effects

The safety profile of the prevention device will affect market share if it differs materially from the safety profile of competing products. Products with fewer side effects and a better safety profile will generally be preferred over those with more side effects. The number and severity of side effects for products included in the overall prevention strategy should be assessed and compared to competing product strategies when determining side effect impact on market share.

Device Use Requirements

The complexity associated with prevention device use will also influence market share. The frequency, complexity, degree of difficulty, and convenience associated with proper device usage will influence a potential user's product preference relative to other product choices.

Local Supply

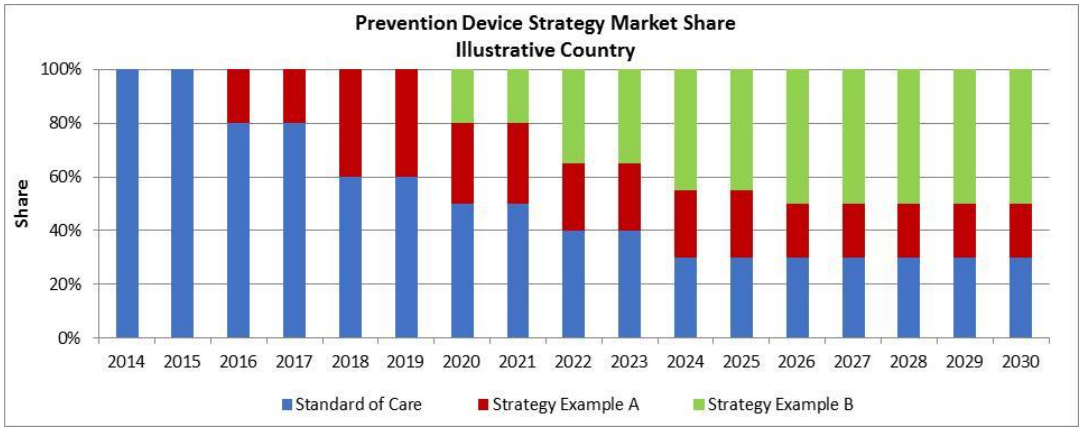
Some countries prefer, or even require, that products be manufactured locally versus imported. Understanding a country's policies on supply origination will be helpful to assessing market share.

Cultural Preferences/Norms

There may also be preferences or cultural norms that affect how various prevention device strategies will be used. Research into preferences will be particularly important for informing peak strategy share. This type of research is increasingly available through social marketing firms in developing countries.

Figure 37 provides an illustrative example of a market share forecast for three prevention drug treatment strategies available within the same country. The SOC realizes a 100% share of the target population until a new prevention drug treatment (strategy A) is introduced in 2017. Share changes further when another new product is introduced in 2020. The decision to prioritize one product over another will depend on which product holds the most desired product characteristics, as described above.

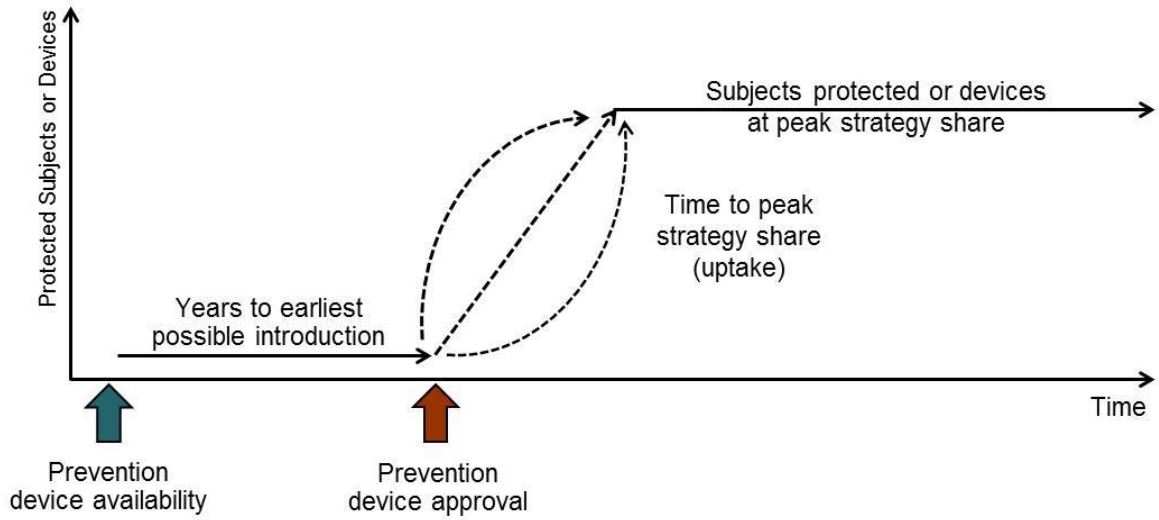
Figure 37: Illustrative Prevention Device Strategy Share Example



Time to Peak Strategy Share

The final assessment required for determining the target population over time, is the device's time to peak strategy share post introduction, which is a country-specific assessment that represents the number of years required to reach peak strategy share, starting from the year of product approval. The time to peak strategy share is influenced by product preference. If the new product is significantly more beneficial than the current SOC, time to peak market share should happen quickly. If the product provides only a small benefit or advantage over SOC, uptake to peak market share may take longer. The protected population forecast is determined by aggregating the population time to peak strategy share curves for all in-scope countries. Figure 38 illustrates a country specific time to peak strategy share curve.

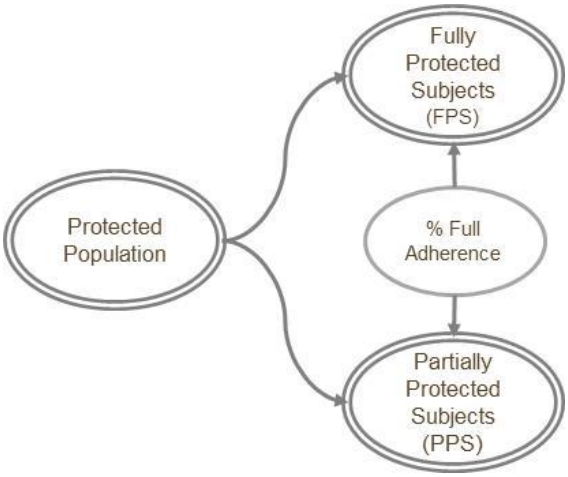
Figure 38: Protected Population Forecast



Fully and Partially Protected Subjects Forecast

How the protected population adheres to the prevention device strategy is the critical assessment for determining fully and partially protected subjects (Figure 39). Capturing the demand required to fully protect subjects is critical and will represent the demand that can actually deliver a health impact. While partially protected subjects are not expected to realize the full effectiveness of the device, the devices used by partially protected subjects are important to capture for supply planning and procurement cost forecasting purposes.

Figure 39: Fully and Partially Protected Subjects Forecast



Percent Full Adherence

The main variable needed to calculate fully and partially protected subjects is the percentage of subjects fully adhering to the prevention device usage requirements.

Percent full adherence is defined as the fraction of the protected population that correctly follows the use requirements. Partially protected patients are the fraction of the protected population that does not fully complete the use requirements. (i.e., 1 - % Full Adherence).

Table 21 identifies several common factors that will influence prevention device strategy adherence.

Table 21: Common Factors that Influence Prevention Device Adherence

Prevention Drug Treatment Adherence Factors
• Device side effects • Direct costs • Device use requirements • Cultural norms

Device Side Effects

The safety profile of the prevention device strategy will have a significant impact on adherence. The types and severity of side effects should be used to assess overall adherence. A review of the product's safety profile, when used alone and in combination with other products, will inform adherence assessments.

Direct Costs

In countries where people pay for prevention devices out-of-pocket, it is important to consider the total price of device use when assessing adherence. Higher priced prevention devices that require frequent use and supporting supplies (e.g., test strips, electrical power) may result in lower overall adherence compared to less expensive devices.

Device Use Requirements

In general, the more frequently the device needs to be used, or the more complex its use, the lower the anticipated rate of adherence.

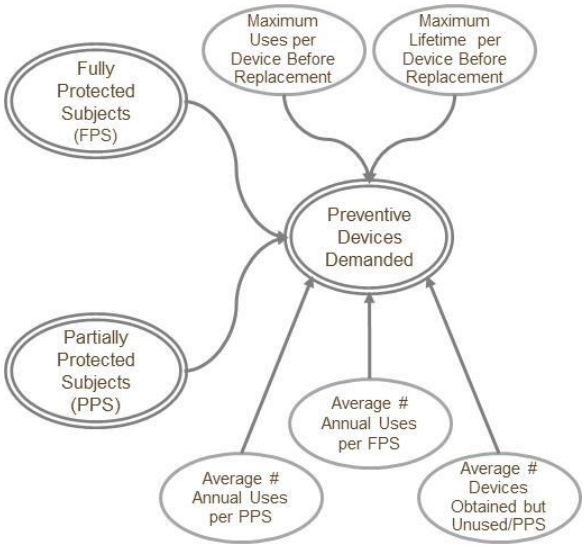
Cultural Norms

There may also be cultural norms that affect how various prevention device strategies will be used. Research into user preferences based on culture or other social/behavioral preferences will be important for informing adherence assessments.

Devices Demanded

The fully and partially treated subjects form the basis for potential demand in number of devices. Figure 40 highlights the input variables required to forecast the number of devices demanded.

Figure 40: Prevention Devices Demanded



Maximum Uses per Device Before Replacement

The maximum uses per device before replacement should be defined in the device's target product profile. Devices may be used once before replacement is required (e.g., condoms) or may be used multiple times before replacement is required (e.g., drug inhaler device that can deliver a specified number of doses before it should be discarded). This variable will be ignored in cases where duration of time defines the useful life of a prevention device (e.g., insecticide treated bed nets can be used as many times as needed over its effective lifetime).

Maximum Lifetime per Device Before Replacement

The maximum lifetime per device before replacement is used to specify when a device must be replaced, regardless of the number of times it has been used. The duration of use is usually a factor of some aspect of the device itself. For example, the insecticides used on bed nets typically have a useful life of two years. This is true whether the bed net has sat in the corner of the room for two years or has been appropriately used every night over that time period. If the useful life duration has been specified for a device, it should be listed in the device TPP or explained in the device user instructions or user manual. It is assumed the effectiveness of the device will be maintained over the specified lifetime.

Average Number of Annual Uses per Fully Protected Subject

The average number of uses per year for a fully protected subject is defined in the intended use statement in the target product profile. It should also be specified as part of the prevention device strategy. The number of uses over a specified time period is important because it will inform the number of devices required to meet the needs of the user. For example, if a device can be used six times before replacement is required, but the user requires 12 uses per year, then the user will require two devices per year.

Average Number of Annual Uses per Partially Protected Subject

Assessing the average number of uses per year for a partially protected subject will inform the number of devices required to meet the needs of the partially protected user. For example, if condom use in the fully protected population is defined as correct and consistent use during every sexual act, and the partially protected population only uses condoms for half of their sexual acts, then the average annual condom usage will be half that of the fully protected population.

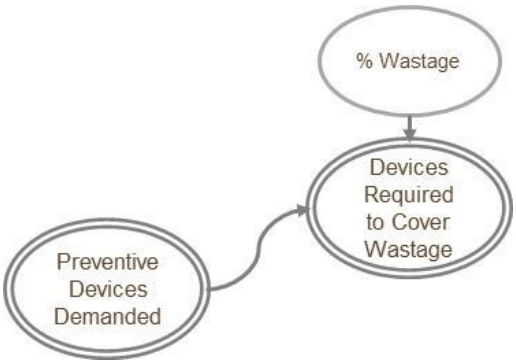
Average Number of Devices Obtained, but Not Used per Partially Protected Subject

The devices obtained, but not used variable accounts for the fact that devices may be purchased (demanded), but not actually used. The percentage not used will be influenced by the usage requirements (e.g., frequency, complexity, convenience). For example, a subject may purchase a box of 10 condoms, but misplace them after only a few are used. If this behavior occurs frequently, the partially protected user may actually be purchasing more devices than required for full protection!

Devices Required to Cover Wastage

Prevention device product wastage can be significant. Therefore, it is important to account for wastage in the final potential demand forecast. Wastage is typically defined as a percentage of the devices demanded for prevention. Figure 41 highlights the relationship between wastage-related input and output variables.

Figure 41: Devices Required to Cover Wastage



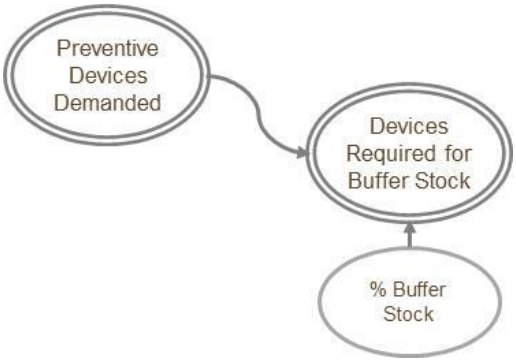
The wastage rate is the percentage of demanded doses (i.e., procured doses) that will be unavailable for prevention purposes because of loss, damage, theft, or inadequate storage. The devices required to cover wastage is equal to the number of devices demanded divided by 1 minus the percent wastage.

Devices Required for Buffer Stock

Buffer stock is the additional device stock kept at the country level to help avoid product stock-outs. Buffer stock provides countries with surplus devices should they be needed to meet faster than expected demand or to mitigate the impact of potential future supply shortages. Figure 42 highlights the relationship between buffer stock-related input and output variables.

Country specific information about the amount of buffer stock procured is often difficult to find. For analysis purposes, buffer stock defaults may be set for each type of prevention device. These defaults are usually applied at the global level, that is, they are applied to all countries.

Figure 42: Devices Required for Buffer Stock



POTENTIAL PREVENTION DEVICE DEMAND FORECASTING METHODOLOGY SUMMARY

The complete methodology for determining potential prevention device demand for a single prevention device is summarized in Figure 43.

Figure 43: Potential Prevention Device Demand Forecast Methodology

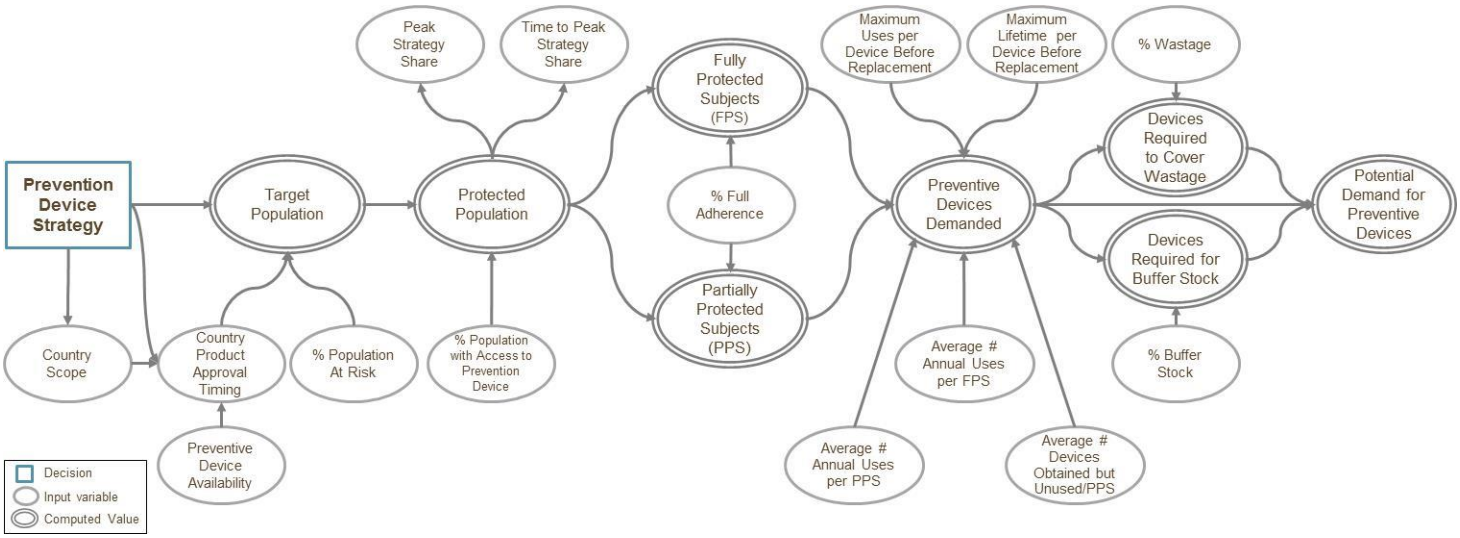
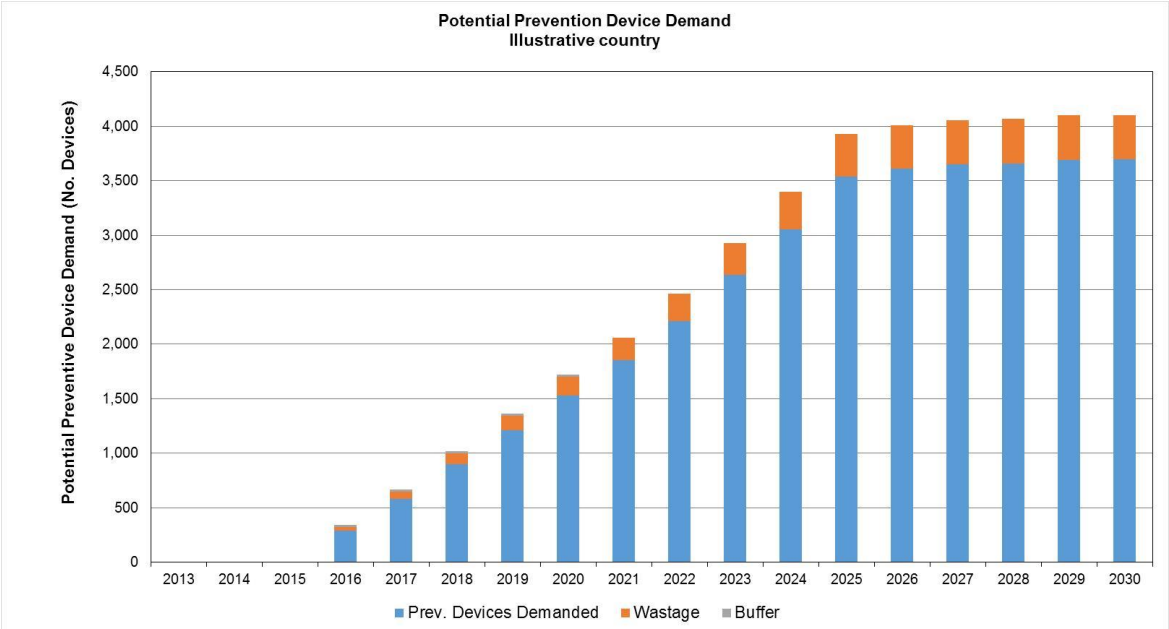


Figure 44 provides an example of the potential demand forecast for a prevention device in an illustrative country. In this example, prevention device uptake increases to peak demand levels in a linear fashion over 10 years. Ten percent of the required buffer stock is purchased in each of the ten years and wastage accounts for the remaining devices demanded.

Figure 44: Potential Prevention Device Demand Example



Diagnostics

DIAGNOSTIC PRODUCT STRATEGY

Potential demand can be forecasted for a specific diagnostic test with one or more points-of-delivery. Diagnostic products often have multiple components that are used to perform a specified diagnostic test. Each potential demand forecast must take into account demand for all of the materials associated with that diagnostic test. These materials may include consumable components, device components, or both. Consumables are materials that are used once during a diagnostic test and are not reused (e.g., test strips, microscope slides, reagents). Devices are product components that can be used in multiple diagnostic tests (e.g., machinery).

To forecast potential demand, every diagnostic product will need a clearly defined diagnostic strategy that will inform where, who, and how to diagnose a particular condition or disease in the field. The diagnostic strategy must include the target disease or condition (what to diagnose), the points-of-delivery (where to diagnose), and a target population cohort (who to diagnose). Each country's demand for a diagnostic product strategy contributes to the overall demand forecast.

When developing the potential demand forecast for a diagnostic, the forecaster should assume operator compliance with the standard operating procedures for the diagnostic test, including proper storage and maintenance of the components, sterile testing environments, and adequate materials, where applicable. The standard operating procedures can be found in the diagnostic product manual or in the WHO Prequalification of Diagnostics Programme Public Report (PQDx PR).

When defining a diagnostic strategy, five key elements need to be specified. Figure 45 describes these five elements.

Figure 45: Diagnostic Strategy Elements

Diagnostic Strategy — Defined by:

Strategy Element	Description	Examples
Target Disease or Condition	Disease , disease combination, or condition targeted by the product candidate	• TB • HIV
Target Cohort Age & Gender	Age and gender cohort that is targeted for diagnosis once the product becomes available	• 14 – 59 year olds • 10 – 14 year old females
Population Subset	Subset of the target cohort based on demographic or user defined characteristics	• Population living in urban slums • IV drug users
Diagnostic Product & Components	Product description including all consumable and device components required to perform a diagnostic test	• Test device with reagents, microscope slides and test kit • Electronic test strip reader with test strips & finger pricks
Points-of-Delivery	Locations where the diagnostic test can and will be used	• Point-of-care (tier 0) • Primary health center (tier 1)

Through the specification of these five elements, any diagnostic strategy can be defined.

Diagnostic Strategy Example

- Rapid (2 hour) test for diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children
  - Intended for use in adults and children who present at tier 2 and tier 3 points-of-delivery (facilities with a reliable source of electricity)
  - Each test requires the use of a sample reagent and tube, sample cartridge with pipette, and testing device (machine)

Diagnostic strategy information, and other important forecasting information, can be found in the Target Product Profile (TPP) and the Integrated Product Development Plan (IPDP). The information gathered from these documents should include, at a minimum, the data highlighted in Table 22.

Table 22: Potential Sources of Diagnostic Candidate Information

Target Product Profile	Integrated Product Development Plan
• Intended use • Target population • Explanation and directions of use • Reagent needs with storage requirements • Specimen collection needs with storage requirements • Sensitivity and specificity of test • Test result interpretation • Potential points-of-delivery	• Current product candidate status • Development phase start date and duration • Estimated date of prequalification

The target population cohort will be specific to an age group and may be gender-specific or target a particular sub-population. Once defined, the target population data by country can typically be sourced from the following reference data:

- UN World Population Prospects (revised annually)
- World Bank, HNP Database Population Projections (revised annually)
- Other data source, as appropriate (e.g., subnational population data, % of population at risk)

The potential Points-of-Delivery (PoD) indicate where the diagnostic test can be performed. The forecaster can choose one or more of the potential PoDs based on the forecasting objective. Table 23 summarizes Points-of-Delivery as defined by the WHO[13].

Table 23: Points-of-Delivery Tier Examples

Tier 0	• Point-of-Care testing at or near the site of patient care; simple tests that can be performed at the bedside and in the field.
Tier 1	• Health post or health center, may be considered “primary care”, usually community centers with a very limited number of beds and few curative and prevention care resources.
Tier 2	• District hospitals, may be considered "secondary care".
Tier 3	• Provincial or regional hospitals, may be considered "tertiary care", includes specialty centers such as teaching and research hospitals or national institutes.

[13] World Health Organization. WHO Global Health Observatory Data Repository. 2014. http://apps.who.int/gho/data/node.main.506?lang=en.

POTENTIAL DIAGNOSTIC DEMAND FORECASTING METHODOLOGY

The methodology presented in this document is focused on the potential demand for a single type of diagnostic test delivered via a specified diagnostic strategy. The methodology, in general, is designed for a disease-specific diagnostic test, however, the forecaster may adapt the methodology for diagnostics used for disease monitoring, such as a viral load or CD4 cell count test for patients with HIV. Because this document focuses on product demand and not health impact, the methodology does not account for complex referral systems or diagnostic algorithms where multiple and different tests are used to confirm diagnoses.

The potential demand forecast will be developed through a series of calculations. Each calculation requires a set of input assumptions that should be clearly documented and transparent to those interested in the demand forecast. Table 24 identifies the calculation components and the key inputs required for each calculation.

Table 24: Diagnostic Calculation Components and Input Requirements

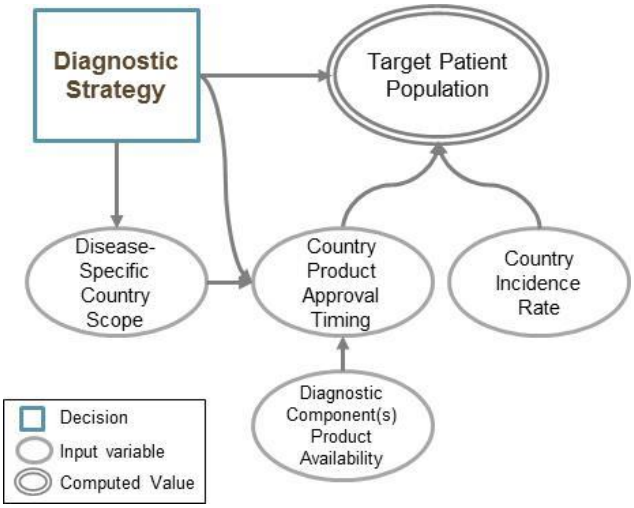
Calculation Component	Input Requirements
Target Patient Population	• Disease-specific country scope • Diagnostic product & components availability • Country diagnostic approval timing • Country incidence rate
Presenting Patient Population per PoD	• Percent of population with access to diagnosis per PoD
Diagnostic Tests Performed per PoD	• Peak strategy share per PoD • Time to peak strategy share per PoD
Device Demand	• Annual device capacity (tests per year) • Maximum use per device before replacement • Maximum lifetime per device before replacement
Consumable Demand	• Consumables per diagnostic test • Consumables % wastage rate • Consumables buffer stock

This document uses simplified “influence diagrams” to provide a step-by-step potential demand forecasting guide. Each section will highlight a piece of the overall influence diagram to help guide the reader through a section at a time. The complete influence diagram will be provided at the end of the drug intervention chapter. Within all influence diagrams, the single lined bubbles represent the input variables that must be assessed in order to develop the potential drug demand forecast. Double-lined bubbles represent calculations (e.g., adding or multiplying two or more input variables).

Target Patient Population Forecast

Figure 46 represents the input variables required to forecast the target population over time. Four input variables are required to forecast the target population for a specific diagnostic strategy.

Figure 46: Diagnostic Product Target Population Forecast



Disease-Specific Country Scope

The disease-specific country scope defines which countries should be included in the potential demand forecast. The country scope should be determined based on disease burden. The country scope may include all countries if the disease is global in nature (e.g., diarrhea) or a specific set of countries if the disease is regionally focused (e.g., malaria, hookworm). Many disease burden sources will identify the highly endemic countries for a given disease, so disease-specific country scope assumptions are not typically considered highly uncertain or difficult to make.

Diagnostic & Components Product Availability

If a country is expected to eventually introduce a diagnostic product, the earliest possible introduction date will be dependent on the availability of the product. A diagnostic is considered available when it has been licensed by a National Regulatory Authority (NRA) for the first time. If there are multiple product components included in the diagnostic strategy, then diagnostic product availability would be the year in which the last of the product components is licensed. This first licensure does not imply that any country can introduce at that time given a country must satisfy its own regulatory requirements before introduction can occur.

Because diagnostic product availability is dependent on the successful execution and timing of the product development plan and the successful completion of supporting activities (e.g., manufacturing scale-up), the timing for product availability can be highly uncertain. Comparing development plan timing assumptions to appropriate benchmarks or similar plans that have already been completed can sometimes help mitigate some of the assessment uncertainty. Accounting for uncertainty by assessing timing ranges for each activity to enable a probability-weighted timing assessment can also help capture the uncertainty associated with product availability.

Country Product Approval Timing

Countries may require national licensure to introduce diagnostics into the public and private sector and each country has its own licensure requirements and processes. For some countries, and donors, WHO prequalification might also be required.

Because diagnostic product availability can be uncertain, country product approval timing methodologies typically define approval timing in terms of years from initial diagnostic availability. By taking this approach, the approval timing will shift appropriately if the product availability assessment is modified.

Table 25 identifies some of the more common factors that may influence country product approval timing.

Table 25: Common Factors that Influence Diagnostic Approval Timing

Country Diagnostic Approval Timing Factors
• Disease burden • National disease policy • Unmet needs

Disease Burden

Disease burden can be a major influencer of country product approval. The greater the burden, the more likely a country will approve a diagnostic if there are no other confounding issues. Country-specific disease burden data can be obtained from a variety of sources (e.g., WHO, IHME). Although each source has its believers and detractors, using the same source whenever possible will mitigate differences based on disease burden methodologies alone.

National Disease Policy

Most countries have national disease policies in place that state the country's control, elimination, or eradication goals. These policies can be used to guide product approval and timing assessments. If a country does not have a national policy in place for a given disease, then approval of a diagnostic might not be considered as high a priority. On the other hand, if a country has an elimination or eradication strategy in place, the country may be highly motivated to rapidly approve a new diagnostic strategy if perceived to be helpful to their disease policy goal.

Unmet Needs

Country approval of a new diagnostic strategy may also be affected by the degree to which the new product is addressing an unmet need. If the specific disease does not have an effective diagnostic strategy, the new product may be more likely to be prioritized for licensure.

Country Incidence Rate

For a given country expected to approve a new diagnostic strategy, the target patient population will depend on the disease incidence rate for that country. The incidence rate is a person's probability of contracting a disease during a given period of time. The incidence rate is usually specified as newly diagnosed cases per 100,000 people. When determining the incidence rate, care must be taken to ensure the incidence rate is for the appropriate target patient population (e.g., children under 5yo; women of child-bearing age). If the incidence rate is not available for demographic-driven cohorts, the forecaster will need to assess an incidence rate given knowledge of the disease distribution by age, gender, etc. Information on the distribution of disease burden in a population can often be found through literature review.

The multiplication of the target patient population by the incidence rate, for a given country, will result in the target patient population.

Presenting Population per PoD

Because diagnostics often require a device and consumables, it is important to know where a specific diagnostic test can be delivered. For example, a rapid diagnostic test can be delivered at the point of care (Tier 0), whereas another diagnostic might require electricity, reagents, and skilled labor to conduct the test (Tier 2 and Tier 3 facilities). Given few diagnostics will be available at all PoDs, the number of diagnostic tests conducted will depend on where patients present themselves for diagnostic services.

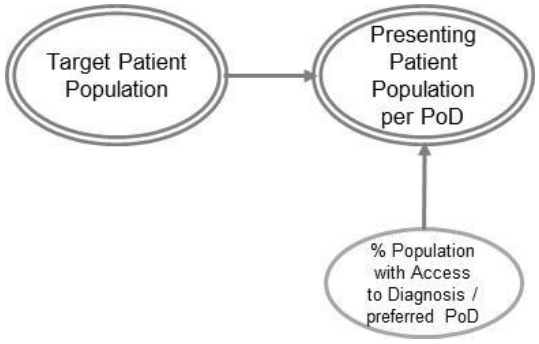
The population with access to diagnosis at a preferred point-of-delivery is the percent of patients who can and choose to access diagnostic services at each defined point-of-delivery. The percent for all points of delivery should sum to 100% of the population wishing to access diagnostic services.

Generalized information about health care seeking behavior is available from sources such as the WHO or Demographic and Health Surveys[14]. More detailed information about care seeking behavior for specific diseases or symptoms can often be found in published literature.

The target patient population may have access to one or more PoDs, therefore, the access assessment should segment the target patient population into what is perceived to be the preferred PoD when given a choice. In most case, the preferred PoD would be the easiest to access (e.g., Tier 0 or Tier 1).

Figure 47 highlights the relationship between the target patient population and the presenting patient population. The presenting patient population is the number of patients that access care at each PoD, regardless of the availability of a specific diagnostic test.

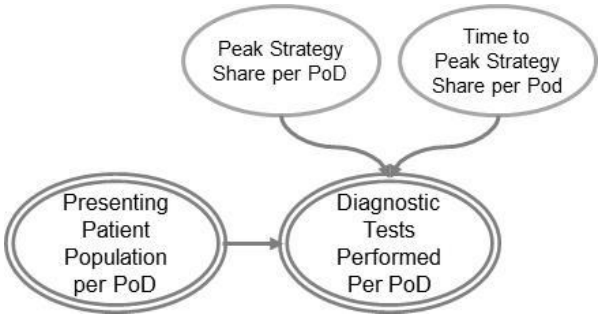
Figure 47: Presenting Patient Population Forecast per Point-of-Delivery



Diagnostic Tests Performed per PoD

The number of tests performed by a specific diagnostic at a given PoD will depend on the percentage of diagnostic tests conducted with that specific diagnostic. Figure 48 represents the input variables required to forecast the number of tests performed over time by a specific diagnostic product per PoD.

Figure 48: Diagnostic Market per Point-of-Delivery



Peak Strategy Share per PoD

The potential demand forecasting methodology accounts for the fact multiple diagnostic products can be available at the same time in the same PoD for a particular condition or disease in a given country. A new diagnostic product entering the market would most likely compete for share with the current diagnostic standard of care, other in-market diagnostics, or diagnostic products currently in development that enter the market at a later date.

When only one diagnostic product is available in a PoD, one would assume the potential demand would be for that particular diagnostic product. If a PoD is expected to have more than one diagnostic strategy available, then market share for the diagnostic product of interest would need to be assessed for each in-scope country.

[14] USAID. The Demographic and Health Surveys Program. 2014. http://www.dhsprogram.com/.

Table 26 identifies several of the more common factors that will influence peak product share for a diagnostic product.

Table 26: Common Factors that Influence Peak Diagnostic Product Share

Peak Diagnostic Product Share Factors
• Diagnostic price • Diagnostic accuracy • Diagnostic test complexity

Diagnostic Price

The cost of the diagnostic test borne by the patient and by the PoD facility will influence product share. A higher priced diagnostic test may not be preferred unless it has demonstrated or perceived benefits to warrant selection over another less expensive diagnostic, including a clinical diagnosis. In cases where treatment of a specific disease is very expensive, a diagnostic product may be used frequently, so as to avert treatment costs whenever possible.

Diagnostic Accuracy

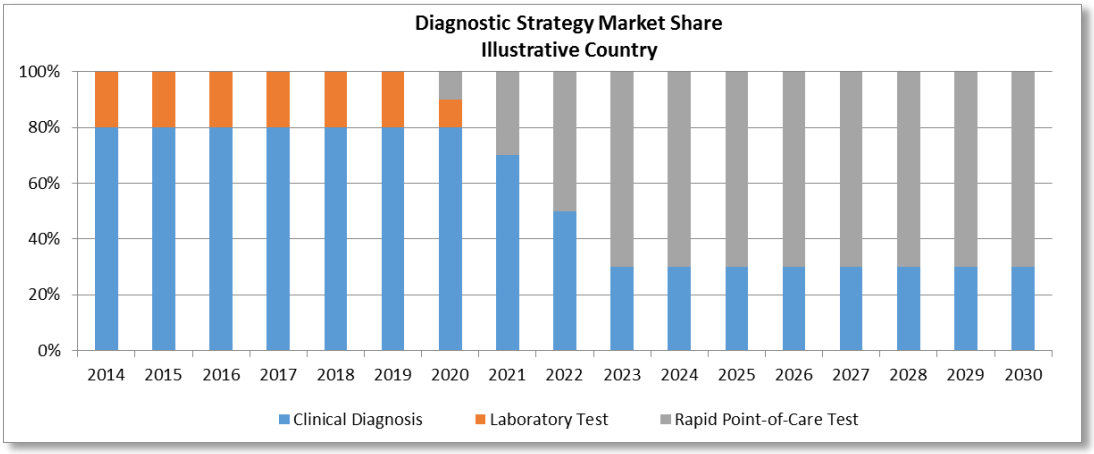
Knowledge of the sensitivity and specificity of a diagnostic product is useful when assessing product share. The more accurate the diagnostic test relative to other diagnostic products or clinical diagnoses will result in a larger product share of the tests conducted.

Diagnostic Test Complexity

The complexity of conducting a diagnostic test will influence product share. Complexity can result from the sampling requirements, the time to test results, the infrastructure and training required to conduct a successful test, or the number of device and consumable components required to conduct the test. For example, a rapid point-of-care test will be much preferred over a test requiring a sample sent to a central lab.

Figure 49 provides an illustrative example of a market share forecast for three diagnostic strategies available within the same PoD within an illustrative country. In this example, clinical diagnosis shares the market with a laboratory test method and a rapid point-of-care test. The rapid point-of-care test eventually renders the laboratory test obsolete, but never completely replaces clinical diagnosis.

Figure 49: Illustrative Diagnostic Strategy Market Share Example

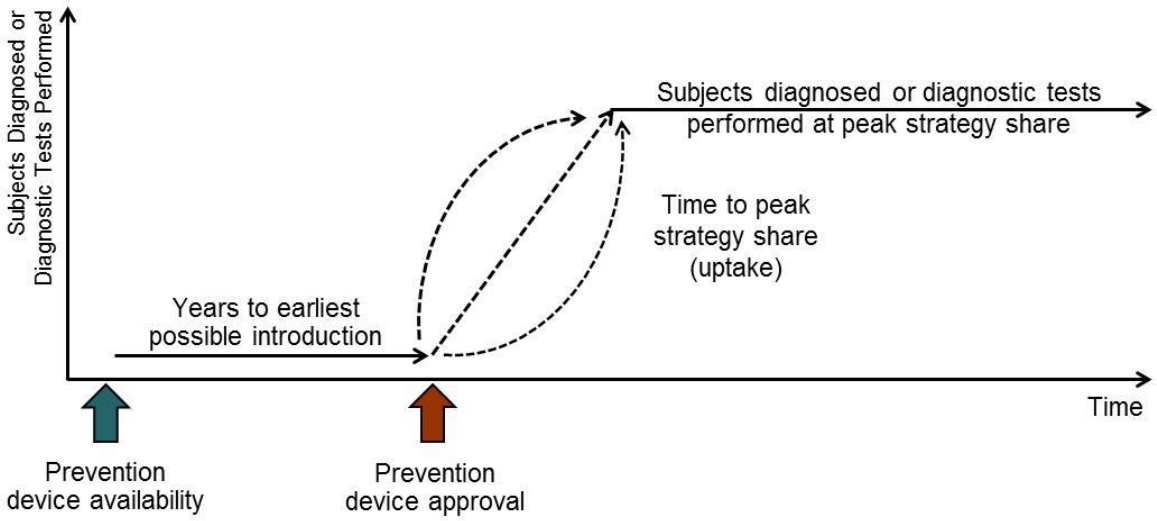


Time to Peak Strategy Share

The final assessment required for determining the diagnostic tests performed over time in each PoD, is the diagnostic product's time to peak strategy share post introduction. This is a country-specific and PoD-specific

assessment that represents the number of years required to reach peak product share, starting from the year of product approval for that country. The time to peak strategy share is influenced by product preference. If the new product is significantly more beneficial than the current SOC, time to peak market share should happen quickly. If the product provides only a small benefit or advantage over SOC, uptake to peak market share may take longer. The diagnostic test forecast is determined by aggregating the product strategy share curves for all PoDs for all in-scope countries. Figure 50 illustrates a country specific time to peak strategy share curve.

Figure 50: Diagnostic Tests Performed Forecast

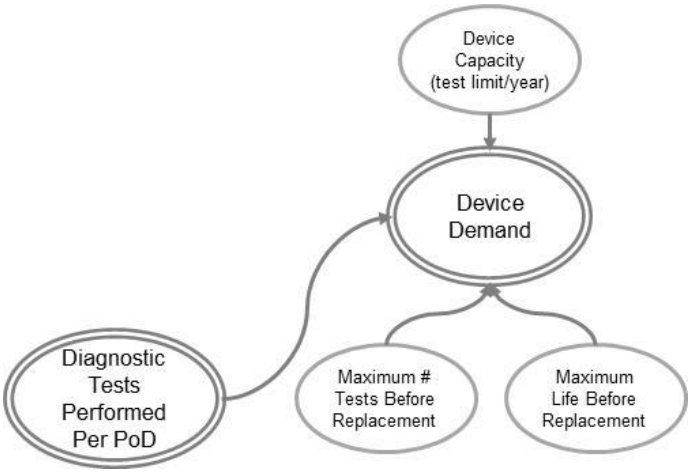


For potential demand forecasts, the actual number of facilities associated with each PoD is ignored in favor of an all-encompassing PoD assumption. Therefore, it is assumed the PoD will have sufficient diagnostic test capacity to address the presenting population. More sophisticated demand forecasts can incorporate actual facility numbers and then account for facility-specific capacity constraints (e.g., test time per patient, electricity outages, consumable supply shortages, staffing shortages). This simplified approach is to focus on what the potential demand could be if constraints were not a factor. Once potential demand is determined, capacity gaps can be identified and investments made to address the gaps.

Diagnostic Device Demand

Demand for the device component of a diagnostic test is dependent on the number of diagnostic tests performed, the device unit capacity, the maximum number of tests that can be performed before the device needs to be replaced, and the maximum lifespan of the diagnostic device before it needs to be replaced. A diagnostic device will need to be replaced whenever one of the maximum constraints is met. Figure 51 highlights the variables that influence device demand.

Figure 51: Diagnostic Device Demand Forecast



Device Capacity (test limit/year)

The capacity of each device is the maximum number of tests that can be performed given the time required to complete each test. For example, if each test requires the device to be used for one hour, then only 24 tests can be conducted in a single day assuming 24 hour testing. If testing is only conducted over an eight hour period each day, then the device capacity is eight tests per day. The device capacity assessment should take into account the testing timeframe per day and the number of days per year that testing is available, as well as any device downtime due to scheduled maintenance or unscheduled repair time.

Maximum Number of Tests before Replacement

The maximum number of tests that can be conducted before replacement should be defined in the diagnostic target product profile. The maximum number of tests before replacement assumes device use and care according to specifications. Diagnostic devices may be used once before replacement is required (e.g., rapid point-of-care diagnostic) or may be used multiple times before replacement is required (e.g., ultrasound wand). This variable will be ignored in cases where duration of time defines the useful life of a diagnostic device.

Maximum Life before Replacement

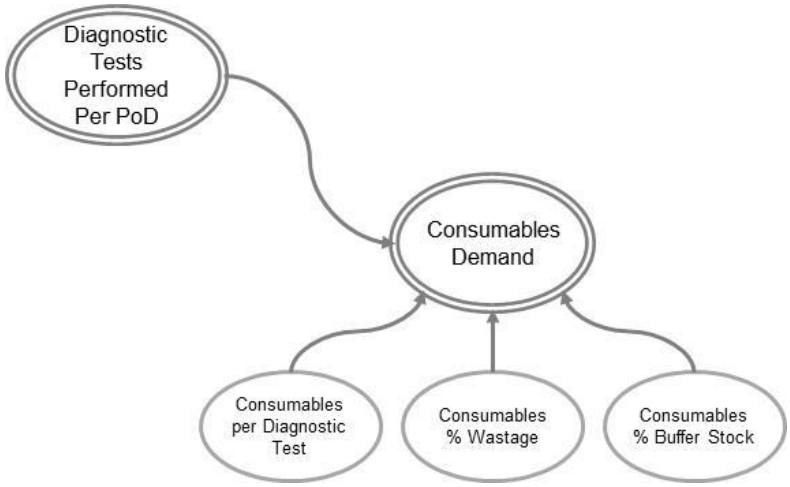
The maximum life per diagnostic device before replacement specifies when a diagnostic device must be replaced, regardless of the number of times the diagnostic device has been used. The duration of use is usually a factor of some aspect of the diagnostic device itself (e.g., part that deteriorates with time). If the useful life duration has been specified for a diagnostic device, it should be listed in the diagnostic device product manual or user instructions. It is assumed the effectiveness of the diagnostic device will be maintained over the specified lifetime.

If a simplifying assumption is made that all diagnostic tests at a specific PoD are conducted in a single facility, the device capacity will dictate how many diagnostic devices will be needed to satisfy that PoD's annual test demand. Additional devices may be needed if the annual device capacity is less than the maximum number of tests that can be conducted before replacement or if the maximum life of the diagnostic device is exceeded before the annual capacity is met. For example, if annual diagnostic test demand is 100 tests and annual diagnostic device capacity is 50 tests, then two devices will be required to meet the test demand. If the maximum number of tests before replacement is 25, then the PoD will need 4 diagnostic devices to meet the annual test demand.

Diagnostic Consumables Demand

Demand for the consumables component of a diagnostic test is dependent on the number of consumable components required per test and the amount of consumables required to cover expected wastage and desired buffer stock levels. Figure 52 highlights the inputs that influence the consumables demand forecast.

Figure 52: Diagnostic Consumables Demand Forecast



Consumables per Diagnostic Test

Some diagnostic products require one or more consumable components to successfully conduct a diagnostic test. For example, some diagnostic tests may require that blood be drawn (requiring a blood collection needle, blood collection tube, sharps disposal box, safety gloves, etc.), and placed in an assay tray (requiring a pipette, assay tray, etc.) for study and diagnosis. Many, if not most, of these diagnostic test components are consumed during the test and cannot be used again. Therefore, the type and quantity of each consumable required for each diagnostic test will need to be assessed.

Information on the consumables required per diagnostic test should be available from the Target Product Profile or the product instruction manual for in-market products.

Consumables Percent Wastage

The consumables wastage rate is the percent of consumables demand that will be unavailable for use due to loss, damage, theft, expiration, or inadequate storage. The consumable required to cover wastage is equal to the number of consumables demanded divided by 1 minus the percent wastage. Wastage rate estimates may be available from published literature, user reports, or supplier evaluations.

Consumables Buffer Stock

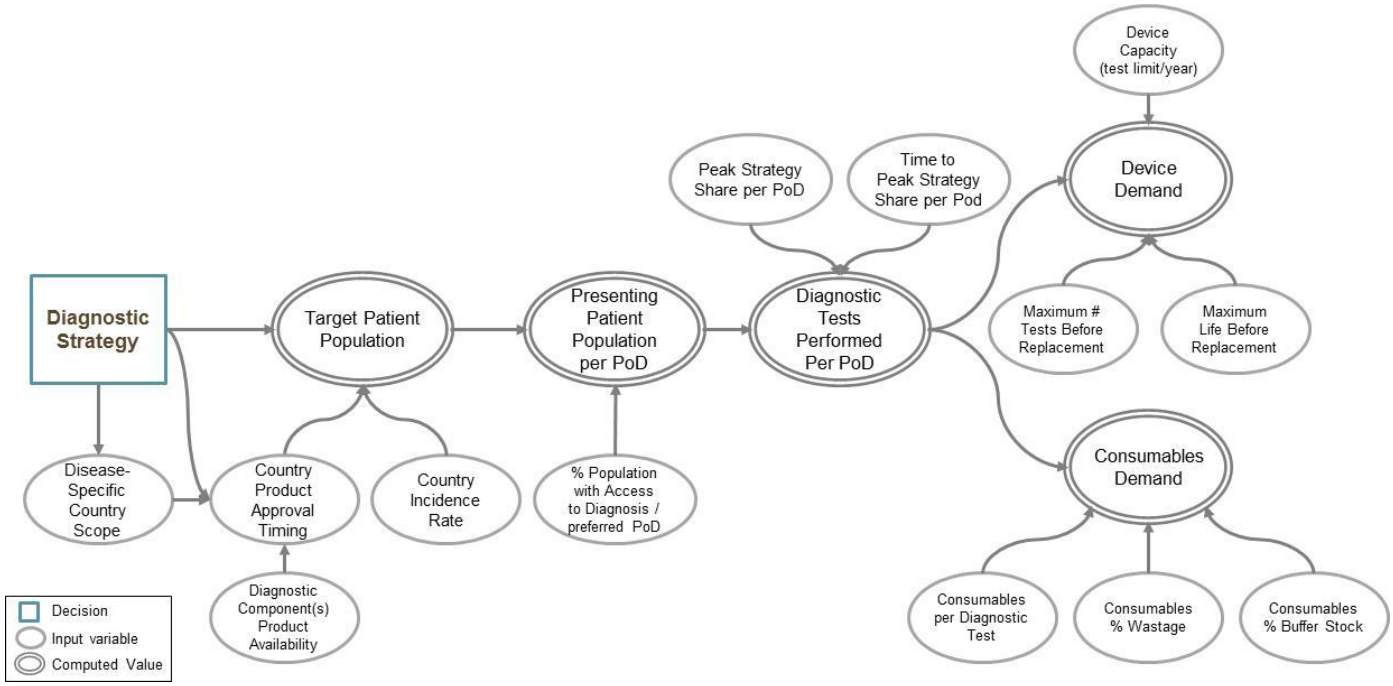
Buffer stock is additional consumables stocked at a PoD facility to help avoid stock-outs caused by unexpected demand, supply shortages or delays, or other unexpected events.

Country specific information about the amount of buffer stock procured is often difficult to find. Buffer stock amounts and rates of replenishment are generally set by country managers at the programmatic level and take into account the storage capacity and shelf life. For forecasting analysis purposes, buffer stock defaults may be set for all consumable products. If demand is highly uncertain, allowing for additional buffer stock may be appropriate.

POTENTIAL DIAGNOSTIC DEMAND FORECASTING METHODOLOGY SUMMARY

The complete methodology for determining potential diagnostic device and consumables demand is summarized in Figure 53.

Figure 53: Potential Diagnostic Demand Methodology



Demand Forecasting Uncertainty

Strategic demand forecasts for global health markets are highly uncertain due to lack of data or poor quality data, extremely long forecasting time horizons, and product and market unknowns. A high degree of uncertainty increases the risks associated with decision making based on forecast outcomes. In general, the farther the product candidate is from entering the market, the greater the uncertainty associated with its demand forecast. Uncertainty in forecasting is unavoidable for many reasons. Disease specific data from developing countries is often not as current, granular, or accurate as that from developed countries. Likewise, information about health care markets in developing countries, such as intervention coverage, access to care, product share, and patient and provider preference, is often much weaker than for developed country markets, though this is changing as this information is increasingly valued by governments and global health organizations. As such, forecasters must often make many assumptions in order to conduct demand forecasts for products targeting these markets.

While uncertainty in demand forecasting is unavoidable, outlining clear and transparent methods and sources for calculating demand can help reduce, or at least capture the uncertainty and mitigate the associated risks. Failing to capture the assumptions associated with demand forecast inputs and assumptions increases the uncertainty of the analysis. As such, it is important to provide a detailed rationale or source that explains where each input assessment came from and why it is being used. This information may actually be more important than the value associated with the variable itself because it provides context that could be leveraged for further research, data collection, and discussion. In addition to the rationale and source, the known or estimated degree of uncertainty should be captured along with the date of the assessment. If desired, an assessment log could be maintained to capture the history of changes made to each variable over time. Long-term strategic demand forecasts should be constantly updated as product candidates move through their lifecycles, and as new data and information become available.

Uncertainty is inherent in most, if not all, of the input variables used in strategic demand forecasting. Capturing the rationale and source of the assessment is the minimum that should be expected to account for the uncertainty surrounding a variable. Capturing the range of potential values for a variable helps forecasters and the forecast audience measure and understand the potential impact that uncertainty might have on the demand forecast output and any decisions it informs. There are several approaches for capturing the uncertainty associated with demand forecasting input variables. Two common methods are described below: (1) deterministic estimate, or (2) probability distributions.

DETERMINISTIC ESTIMATES

A deterministic estimate or variable is characterized as a "base" value or a set of values over time that represent the most probable or expected value of the variable. For example, this may represent the "most likely scenario". The level of uncertainty of the variable is captured in the assessment rationale. However, assessing a single value for a highly uncertain, or simply unknown variable can be difficult and the choice of value may be very influential to the outcome of the analysis. Including additional deterministic values in the assessment can provide a way to explicitly capture the "range" of uncertainty that is associated with the variable. These additional assessments may come from various data sources and are most typically values that represent a "best case scenario" and a "worst case scenario." Capturing additional rationale and source documentation supporting the choice of high and low deterministic assessments is highly recommended. With a range of values for each variable, deterministic sensitivity analysis can be performed to provide the forecaster and the forecast audience with an indication of which of the input variables has the greatest impact on overall demand.

PROBABILITY DISTRIBUTIONS

In a probability distribution, variables are captured as a distributed set of values that represent the uncertainty across all possible outcomes. The uncertainty represented by the selected or assigned distribution is captured in the rationale of the variable assessment. The variable could be a continuous or a discrete variable.

If the variable is discrete, then each possible outcome of the variable is identified (i.e., mutually exclusive and completely exhaustive outcome set), and a probability for each outcome is assigned. The sum of all probabilities must equal 100%. The "base case" of the set of outcomes is then assigned, often defaulted to the highest probability outcome.

If the variable is continuous, then a common distribution (e.g., Uniform, Bernoulli, Binomial, Poisson, or Normal) can be selected. If a common distribution is selected, then the parameters of that distribution should be used in the demand forecast calculation. However, it is likely a traditional distribution will not be known for every input variable and thus a simple approach to representing the range of uncertainty inherent in the variable is needed.

A 3-point distribution is the simplest way to capture uncertainty. A 3-point distribution would consist of a High, Base, and Low outcome value, similar to the discrete estimate, where each outcome value would also have an associated probability with the total summing to 100% (e.g., 25%, 50%, 25%). Each of the distributions would have a mean, representing the "base case" value in the analysis. The forecast would also provide outputs representing the 10^{th} and 90^{th} percentiles, which could then be used for computing a deterministic sensitivity analysis. In addition, probabilistic or Monte Carlo analysis could be conducted.

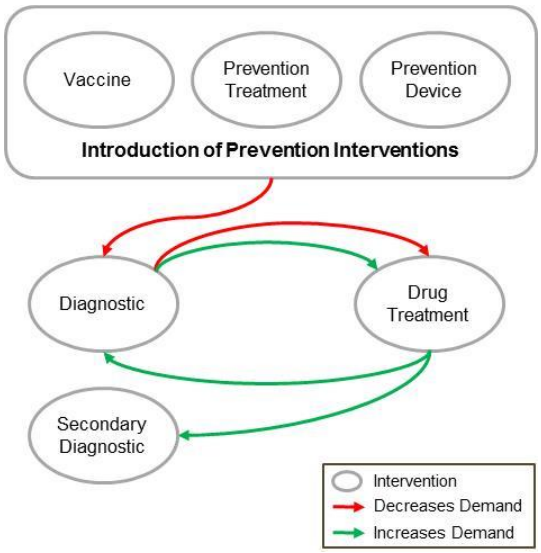
Regardless of the approach by which uncertainty is captured, clearly outlining transparent and evidence-based methods and principles for demand forecasting can help reduce the inherent risk and uncertainty associated with assessing future demand, particularly in developing country markets. Risk transparency leads to more credible forecasts and more thoughtful decision making.

Cross-Intervention Interaction

This document presents a generalized methodology for forecasting the potential demand of health interventions ignoring potential funding or supply constraints. The methodology also does not incorporate possible interactions between intervention types. These complex cross-intervention relationships are more appropriately addressed in product-specific valuation methodologies, rather than in high-level, strategic demand forecasting methodologies. We can still anticipate and document the likely relationships between prevention, diagnostic, and treatment interventions with the goal of more accurately reflecting these relationships. The resulting changes in demand can be accounted for when more sophisticated methods and models are available.

Increased demand, and ultimately use, of prevention-focused interventions may decrease the disease burden or transmission of a disease, thereby lowering the demand for diagnostics. As the demand for diagnostics decreases, the demand for treatment can increase or decrease, depending on the characteristics of the disease and any previously available diagnostic methods. For example, if the diagnostic product significantly reduces the number of false positive diagnoses, this would, in theory, lead to a decrease in treatment demand. Alternatively, if no diagnostic method was previously available, a new diagnostic product can increase demand for treatment due to a greater number of accurately diagnosed cases. In some cases, treatment leads to further use of confirmatory or secondary diagnostics, thus increasing the demand for complementary and follow-on diagnostics. Depending on the characteristics of the disease, this cycle may eventually lead to disease elimination or eradication, thus reducing the demand for all interventions. Figure 54 illustrates at a high-level these potential cross-intervention interactions.

Figure 54: Potential Cross-Intervention Interactions



There are exceptions to all of the proposed relationships. For example, vaccination to prevent human papillomavirus (HPV) does not directly reduce the use of Pap smear diagnostics, though vaccination will prevent infection, related sequelae, and reduce the need for future treatment. In most cases, health policy and patient and practitioner preference influence demand for diagnostics and treatment. The prevention, diagnosis, and treatment of a disease may vary widely between settings due to resource limitations, and health policy and systems. Forecasters need to carefully consider the context of the intervention when assessing inputs, potential intervention interactions, and interpreting demand forecast results.

Demand forecasting is one element of evidence-based portfolio management. Additional analyses may include, but are not limited to, the health impact and cost-effectiveness of the interventions. These analyses are dependent on the outcomes of the demand forecasting exercise. Each intervention can have a direct health impact (e.g., prevention of disease, mortality, death) and an indirect health impact (e.g., herd immunity, cross-intervention

impact, such as decreased demand for drug treatments). To predict the health impact and cost-effectiveness of an intervention for a particular condition, disease, or disease combination, all concurrent efforts for prevention, diagnosis, and treatment of the disease should be considered. For interventions aimed at directly preventing or treating a condition, disease, or disease combination, such as vaccines and drugs, the flow from demand of an intervention to its health impact is relatively organic. Persons benefiting from the intervention are assumed to have some positive health impact due to fully or partially compliant use. The health impact of diagnostics, however, are typically linked to a future treatment that results from a positive diagnosis. In this case, the dynamic relationship between the two interventions needs to be considered.

Cost-effectiveness provides a comparable metric of the health impact of an intervention per dollar invested. As described above, interventions can have direct or indirect health impact. The introduction or increased demand of an intervention is associated with an increased procurement and delivery costs. To correctly estimate the cost-effectiveness of interventions, the forecaster must consider the relationships between the interventions, disease dynamics, costs incurred to provide the interventions (e.g. procurement and delivery costs), and any averted health care and treatment costs. Typically vaccines and prevention drug treatments and devices have positive health impacts (e.g., prevent disease) and ideally decrease the need for diagnosis and future treatment. Diagnostics rarely have a direct health impact, but may affect treatment outcomes and costs, thus having a 'down-stream' impact on cost-effectiveness. Therefore, forecasters should evaluate demand, health impact, and cost-effectiveness within the broader context of the disease of interest and the interrelationship between available and expected interventions.