DESIGN,
ANALYZE,
COMMUNICATE DAC

Target Policy Profile

Version 2, May 2023

Contents

Section 1: Target Policy Profile (TPoP) Overview

Introduction

The Target Policy Profile (TPoP) is a tool to aid discussion on the evidence needed to change or establish a new policy. This policy could be at the country, regional, or global level. The TPoP should state the proposed policy, the supporting evidence, gaps in the evidence, and the nature of evidence required to fill these gaps. The TPoP should serve as a framework for dialogue and alignment between key stakeholders in the policy development process. By laying out a roadmap to intended policy impact, this tool can also support funding decisions for a particular research agenda.

Who should complete the TPoP?

A TPoP engages and aligns stakeholders who have an interest in the proposed policy. A TPoP can be completed by those governing the policy (e.g., the World Health Organization) or by one or more groups who wish to engage and align with the stewards of the policy. Typical stakeholders include research funders, researchers, governments, patient consortia, pharmaceutical companies, manufacturers, and those subsidizing or distributing interventions relevant to the policy. Policymakers and/or research funders may have technical advisors or access to subject matter experts who could support completion of a TPoP. It is unlikely that single authorship from a researcher will have the greatest impact. Collaborative development of the TPoP is encouraged, including from consortia or stakeholder groups.

When should one be completed and how is it kept up to date?

A TPoP should be completed whenever a change in policy is proposed. It should be updated whenever significant new information becomes available that may affect any of the statements within the TPoP. A TPoP should be kept current throughout the lifecycle of the policy change. More guidance on the timing of TPoP development by intended use case is available in Table 5.

Who is the audience for a TPoP?

A typical target audience is the policymaking body that decides if, when, and how to change policy on how to address a health condition. This body is often the World Health Organization (WHO) and/or ministries of health. Research shows that inclusion of policymakers when designing research is a key factor associated with a change in policy (Theobald, et al. 2018, Hanney, et al. 2003, Yamey and Volmink 2014, Innvaer, et al. 2002).

However, it is not always possible to directly engage those responsible for a change in policy. In these circumstances, stakeholders can use the TPoP to discuss policy considerations and agree on the current state of knowledge and research gaps. The TPoP may also be used to activate funders towards these identified research gaps. If a discussion on global health policy options is happening, the ideal centerpiece is a recent and thoroughly completed TPoP.

Non-experts should be able to understand the wording used in a TPoP. Researchers have found that “scientific rigor” is negatively correlated with uptake of research findings into policy. They suggested, “it is possible that policymakers are not so much opposed to scientific rigor in research as ‘alienated’ by impenetrable technicalities and academic jargons” ” (Liu, et al. 2018). Knowing the intended audience for the detailed TPoP is a critical success factor and should be considered before beginning the creation exercise.

Section 2: TPoP Template and Brief Instructions

Engaging your target audience early and often

First, you should identify the target audience for the policy you want to discuss. Often, policymakers are the target audience. An ideal approach is to engage specific members of your target audience as well as key opinion leaders in early dialogue. For example, include them in a policy design workshop to identify the key points for your case for change and collaboratively fill in **Table 1 (TPoP Summary)** and **Table 3 (TPoP Case for Change)**.

The second step is to complete a first draft of **Table 2 (TPoP Tool)**. This tool summarizes the evidence for the current and proposed policy, with pros and cons for making the change. The TPoP can then be iteratively revised. Revisions should be based on new research findings and on ongoing collaboration with relevant stakeholders.

Drafting your TPoP

In this section you will find three tables that will help you and your stakeholder groups draft your TPoP.

Tables 1 and 2 are the summary and detailed sections of the TPoP, respectively. They provide a comparison of the proposed policy, the current policy and the pros and cons of making the change. The completed tool should summarize evidence in non-technical language. Detailed information about each of the fields in the TPoP tool is in Section 4 of this document.

Table 3 (TPoP Case for Change) includes a list of categories and prompts to help you assemble your case for change. This will describe why a new or updated policy is needed, risks and benefits, and implementation considerations. It is likely you will need to first answer these questions before filling out **Table 2 (TPoP Tool)**. Not all may apply to your specific context. You may also convert this table into a narrative executive summary to engage policymakers, the research community and/or other stakeholders. A guide to this conversion is in Section 4.

Appendix A provides a completed TPoP exemplar for a proposed HPV single-dose policy change.

Table 1. Target Policy Profile Template **Summary** Information

Target policy name:	
High level policy currently in place (if applicable):	
Target audience:	
Key stakeholders:	
Authors:	
Consulted parties:	
Date of last revision:	

Table 2. Target Policy Profile Template **Tool**

	TPoP fields	**Target policy proposed and attributes of product(s)**	**Current policy/ Standard of Care**	**Pros / Cons**
1	**Indication, disease, condition**			
2	**Target population**			
3	**Intervention, product, dose**			
4	**Delivery strategy for intervention**			
5	**Efficacy, effectiveness**			
6	**Fairness, equity, acceptability**			
7	**Other considerations**			
8	**Safety**			
9	**Implementation**			
10	**Feasibility, practicality**			
11	**Guidelines, Standard of Care (SOC)**			
12	**Policymaker engagement**			
13	**Communication and convenings**			
14	**Political factors**			
15	**Costs, affordability**			

Table 3. Target Policy Profile Template **Case for Change** (with prompt questions)

	Description of current policy and approach	• What are the details of the current approach to the health problem?
1	**Existing WHO guidelines relevant to target policy**	• What guidelines already exist relevant to the health problem described? • What type are they (e.g., standard, interim, rapid) and when were they published? • Are there any active or planned guidelines updates taking place?
2	**Proposed change**	• What details of the current policy are you proposing to change? • If relevant, when was the current policy created?
3	**Reason for the change**	• What are the challenges with the current policy? • Why would a new policy be better than the current policy?
4	**Existing evidence supporting a proposed policy change**	• What evidence (providing full details), often in the form of randomized controlled trials, already exists to support the proposed change to the policy?
5	**Benefits of new policy**	• What are the specific health benefits of switching to a new policy? • What are the specific benefits outside public health (e.g., costs) vs the old policy?
6	**Risks of new policy**	• What risks could there be of changing to the new policy?
7	**Limitations of existing evidence**	• What gaps exist in the current evidence base? • Why might existing evidence not generalize to our population? • How clear & informative is research to date? • What is the current evidence on benefits or harms?
8	**Evidence needed to achieve the policy change**	• What questions, if answered, would call for a new policy? • What evidence is needed to answer these questions? • What research has been requested by key policymakers? • What are the gaps in evidence that require further research?
9	**New or upcoming evidence**	• What new studies have been completed that provide evidence supporting the proposed change in policy? • What additional studies are currently underway or planned to provide relevant evidence?
10	**Generation of further evidence to fill gaps**	• What is the plan to address the identified gaps? • Are there new or follow-on studies that could be completed quickly?
11	**Qualitative health benefits**	• What social, political, or quality of life benefits are expected? • What benefits exist in other populations who have the new policy?
12	**Quantitative health benefits and cost-effectiveness considerations**	• How many lives saved, or quality-adjusted life year (QALY) benefits come from the new policy? • What costs must be invested to achieve those savings?
13	**Target countries**	• In which geographies would this policy be implemented? • What variables define which areas to target first?
14	**Time and costs to implement**	• How long would it take to ramp up the new policy?

		• What are the high and low cost estimates over what period? • Are there any implementation barriers already identified? • Who might be the key funders to support the new policy in pilot phase and beyond? • For national policy discussions, what government funding might be available and which department is critical to include in discussions?
15	**Feasibility and who is involved in generating the data**	• How simple or complex is implementing the new policy? • Who has done a feasibility / practicality analysis? • Who is addressing the gaps in the evidence?
16	**Regulatory considerations and PQ, are relevant products eligible for PQ**	• What is the regulatory path? • What regulatory issues or hurdles will need to be met? • What types of qualification have been met or need to be met?
17	**National considerations in target countries**	• What national considerations need to be taken into account related to this proposed policy change, including long-term budget planning and/or capacity to implement? • What current political factors might affect perception if policy changes?
18	**Delivery and implementation considerations**	• What stakeholders, organizations or partners are involved in delivery? • Have any pilots been performed to define implementation?
19	**Ongoing monitoring after the policy change**	• What is the monitoring and evaluation strategy? • Who will measure if the health benefits reach the new policy targets? • What will need to be monitored (e.g., drug resistance, variants)?
20	**Process and timeline for policy engagement**	• Which specific policymakers will be engaged? • What is the duration and roadmap for achieving policy change?
21	**Proposed plan going forward**	• What is your action plan and timeline including evidence generation, compilation, presentation to policymakers through to policy change and implementation?
22	**Existing use of the proposed policy**	• Is there any setting already using the proposed policy? • Describe any pilot projects employing the proposed policy. *See Section 4 for more detail.*
23	**Minimum Policy Important Difference (MPID)**	• What is your MPID and rationale for selecting it? • What is the smallest value judged to be both detectable and meriting policy change? *See Section 4 for more detail.*

Section 3: TPoP Background and Key Considerations

Introduction

A primary goal of clinical research in global public health is to create, test, implement, or monitor the best interventions. If a new intervention proves much more effective than the current standard of care (SOC), people will benefit when that SOC is updated to the new intervention. This is to enact public health policy. Public health policy consists of laws, regulations, decisions, and actions taken to promote and ensure specific health care goals are met.

Proactively mapping a clinical research study's outcome to public health policy is complex. The Target Policy Profile can simplify, standardize, and speed up the transformation of informative clinical research results to new or updated policy. It can be used at a point of evidence generation and dissemination to make the case for policy change. The TPoP can also be used before research to define unanswered questions to support policy decisions.

While some global health stakeholders might have experience engaging with policymakers, most do not. Having a tool in hand to frame the dialogue is a crucial asset. The TPoP may be most valuable not as a dissemination tool, but as a structure to frame discussions with policymakers. The TPoP can help all stakeholders understand what policymakers need to inform their decisions.

Background: the Target *Product* Profile

In 1997, Drug Discovery Today published a paper describing an internal tool gaining momentum among drug makers as a "design specification for the product" (Kennedy 1997). The tool described, the Target Product Profile (TPP), has become a global standard driving decisions that touch millions of lives (Figure 1). The TPP has become commonly used across the WHO. Regulatory stakeholders also use it as a mechanism to align, communicate, and collaborate with pharmaceutical manufacturers.

Figure 1. A common format for classical TPPs (Brooks, et al. 2012)

Product class:						
Product name:	*To be completed once product approaches phase 2b*					
Date of TPP endorsement						
Dates of TPP revisions						
	Desired		**Minimally acceptable**		***"Insert Product Name"* profile** (Completed as product approaches phase 2b)	
	Target	**Rationale**	**Target**	**Rationale**	**Target**	**Rationale**
Indication						
Expected efficacy						
Target population(s)						
Route of administration						
Formulation & presentation						
Dosage schedule						
Safety profile						
Co-administration						
Shelf-life & storage						
Manufacturability						
Price						
Product registration and WHO prequalification						

Background: the Target *Policy* Profile

The Bill & Melinda Gates Foundation introduced the term "Target Policy Profile" in 2017 to describe a tool for progressing from a medical innovation to a social policy or service (Grasela 2017). While the TPP is a tool for agreeing on key attributes a product needs to achieve, the TPoP is a tool for agreeing on what is necessary from a medical innovation to achieve a change in policy. While the term was first mentioned in 2017, no package of attributes or sections was published at the time. In 2020, the TPoP was released publicly (Dolley, et al. 2020). In 2021, the WHO was introduced to the tool, and used it as a basis for their Evidence Considerations for Vaccine Policy (Kochhar, et al. 2022).

Policy Details

Whereas a TPP provides a *product* specification, a well-developed TPoP may act as a *policy* specification. That is the aim. The TPoP should lay out the evidence requirements and technical information necessary to see how an intervention would be implemented, funded, and regulated. It should also show how the intervention will affect citizens and patients. The detail should inform many stakeholders:

- clinicians establishing clinical guidance
- distributors or retailers managing supply chains
- public health departments administering mass drug administration, spraying or other control or testing mechanisms
- pharma or device manufacturers producing interventions
- regulators imagining success of existing pharmacovigilance, quality, licensing, and other programs with regards to the new policy.

Some attributes from the TPP can carry over to the TPoP. This might serve as a bridge to an intervention scheme laid out by a TPP. An actor could then move back and forth between the world of intervention and policy. Future efforts in this space may include fostering alignment on the minimum acceptable and the ideal attributes for both a TPP and TPoP. Joint use of these tools, with shared terms and definitions, could support faster decision-making and ultimately speed up an intervention's impact.

Additionally, the policy details of the intervention may be informed by a Health Technology Assessment (WHO 2020). While it includes the word "technology", it is applicable to any health intervention.

> *"Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner."* (European Network for Health Technology Assessment 2020)

HTAs include thorough and systematic diligence to inform policy, coverage, and reimbursement decisions. TPoPs focus on research and development findings that could change policy, and the drivers and consequences of policy change.

TPoP Focus

A completed TPoP tool (**Table 3**) should:

- be broadly applicable, or cover a specific policy, region, population or point-in-time situation
- be authored by any of a wide range of types of stakeholders, including global guidance bodies, researchers, policymakers, regulators, funders, industry, non-governmental organizations implementing the change, or others
- tie to one or more diseases and/or interventions

- integrate with specific instances of clinical guidance, health system policy, environmental actions, supply chain standards or operating procedures, regulation, and TPPs
- answer questions for policymakers on the implications of the proposed policy change, such as why, how, when, where, and how much
- be discussed with those responsible for the policy, ideally as part of the TPoP creation.

A 2018 update on implementation research in global health in *The Lancet* included this:

> "*Policy makers, funders, implementers, researchers, and community members each view problems differently. Wendy Graham of Aberdeen University famously characterized these differences as 'Researchers are from Venus. Policy makers are from Mars.' …As a simple example, policy makers often do not require a confidence of p<0·05 to make a decision and might hesitate to expand a sample size or the duration of a study simply to meet this threshold"* (Theobald, et al. 2018).

A study on whether research can change policy concluded: "the evidence of widespread, direct impact on policy…is at best patchy" (Hanney, et al. 2003). This may be because "health policymaking involves an uneasy balance of science, economics, and politics" (Yamey and Volmink 2014). When researchers engage in sharing results and attempting to participate in the "uneasy balance", this is often called knowledge transfer and exchange (KTE).

A sample of questions a policymaker or government official may want to answer during their decision-making process and KTE is listed in Table 4. These questions and related objections give a window into the thinking that may be occurring in the minds of policy stakeholders. Knowing the research results that will move "all-impact thinking" to a policy change is the crux of the TPoP.

Table 4. All-impact Thinking by Policymakers

Type	Questions	Objections
Why	Why change policy? Why defund other programs to pay for the increased costs of this new policy?	We have a perfectly good SOC already. This problem is not so significant. The affected population is only a fraction of our state. It will be more expensive, so the funding must be pulled from elsewhere to pay. But those other programs are in place, expected by citizens.
How	How do we implement this change? How will my population feel about this change? Will it change how they vote in the next elections? How will the media cover this change? How will the risks be managed?	Such a change would be disruptive. The political climate is not ready for such disruption. If it fails, the negative media coverage will almost require a change in political leadership. It is not clear we could implement such a change as well as other countries.
When	When do we need to start? When will the changeover be completed? When will the public's patience be exhausted if we don't make new medicines or policy available?	It will take years to implement. If we wait for other countries to implement the change, we will be able to see the effects and resistance. This will be more practical to implement later.
Where	Where do we start? Is this change for all the geographies in my population?	Some regions will feel disenfranchised. The indicated group is only a fraction of the population. Those affected may not have participated in convenings to date. The treated area may not include my voters.
Who	Who will be treated? Will those treated include those who vote for me? Who is receiving the funds for the new intervention? Who provides the current intervention and may lose funding?	I don't know or trust the people who invented this new innovation. I haven't spent time with the researchers who are pushing the new policy. Our usual global partners may not co-fund this for us. With the new scheme, my voters may not receive treatment.
How Much	How much will it cost? How much benefit do we receive vs. what we have today? How much of the cost investment is received by what types of stakeholders?	This will be very expensive. It will likely cost more than is estimated. The number of lives saved is only a prediction. The global North is receiving an inordinate share of the cost investment involved.

Case for Change

The TPoP will establish arguments based on robust evidence for why the proposed policy change will save and improve lives. It will summarize the existing approach and propose the evidence and implementation requirements to justify the proposed policy change. This evidence will come first from new research. Additional evidence may come from implementations, pilots, and guidelines. The TPoP will highlight existing research and describe any gaps further studies should fill. The TPoP will serve as a tool to discuss and agree on approaches and actions including the design of studies to address evidence gaps. The TPoP will aim not to position missing research as a blocker for policy change unless it truly is the driving reason for inaction.

Implementation research and policy change capacity in low-income countries have advanced, but unmet needs persist. New tools are emerging to meet the ongoing need. Some may be helpful for preparing a TPoP and the underlying case for change (Dodd, et al. 2019, Milat, et al. 2020, Pottie, et al. 2019). Examples include: the Intervention Scalability Assessment Tool (Milat, et al. 2020), which may be immediately applicable to a low resource setting policy change; Grading of Recommendations, Assessment, Development and Evaluations (GRADE 2023); and the Evidence to Decision framework (Alonso-Coello, et al. 2016). Another tool called CERQ-Qual helps policymakers gain confidence in systematic review-based evidence (Lewin, et al. 2015). Finally, some practitioners believe in using a low resource setting-adjusted Consolidated Framework for Implementation Research to augment a TPoP (Means, et al. 2020). These tools may help decision makers feel confident in processing new scientific data and understanding potential actions, benefits, and costs.

A TPoP can be defined according to primary need. In most cases, the goal will be to tell the story of the benefit of a new proposed policy, or to make a case for change. The full TPoP document should start with an executive summary followed by the anticipated benefits of a new policy. If possible, it should include an exemplar case of how the policy is performing well in any current use. It may also note challenges of the current policy that make the newly proposed policy attractive to public health.

TPoP Use Cases

The TPoP will be helpful when updating or creating new policies. Depending on the circumstance, certain sections of the TPoP become more important. Some use cases are listed in Table 5.

Table 5. TPoP Common Use Cases

Use Case	When in the process	Participants	Most important TPoP section
Using the TPoP to facilitate generation of new, primary evidence through solicitation of new dialogue, with new voices	At any time before, during, or after the key study of interest or the policymaking process	The widest group that is feasible, toward adding new voices. Beyond researchers, policymakers, and implementers, include voices of the patient, and policy and research enablers	All sections
Prior to evidence generation or beginning the research study in consideration, identifying what new evidence policymakers need to feel comfortable changing to a new policy	At the beginning of a process that ends with adoption of a new policy	Researchers, implementers, and policymakers	Evidence (i.e., Table 3 rows including existing evidence, limits and gaps)

Use Case	When in the process	Participants	Most important TPoP section
After evidence generation – the completion of a key study or studies of interest –, going back to policymakers to make the case to act now to change policy	Late-middle in the process that ends with adoption of a new policy, when no further studies may be needed if policymakers are satisfied	Researchers, policymakers, pharmaceutical companies, developers	Evidence, Target policy proposed (i.e., Table 3 rows including evidence, and Table 2 target policy column)
To get a medicine unstuck from an "in limbo" place where no further investment will be made without policymaker commitments	Before, during, or after Phase IV, where policymaker concerns are blocking any further progress	Policymakers and pharmaceutical industry, with some participation from researchers or other groups	Specific to identified policymaker concern (e.g., product availability, affordability)
After the decision to adopt a new policy, planning on how to implement the new policy	After the decision has been made to implement a new policy	Policymakers, implementers including non-governmental organizations (NGOs), government officials, pharma or device makers, health economists	Target population, fairness, equity, costs, implementation, feasibility, practicality
To complement WHO Norms & Standards existing tools, such as Evidence to Decisions, GRADE, or Health Technology Assessments	After key evidence has been generated by studies of interest, and during the policymaking process, if or when policymakers need additional inputs for their existing tools	Policymakers, researchers	Section specific to the identified policymaker/ guideline creator's concern(s)
As input to the refresh of a disease guideline publication or new disease guideline publication from the WHO 7	When a guideline panel is beginning their evidence synthesis phase, and could request a TPoP completion	Policymakers	All sections

Section 4: Detailed Instructions for Completing the TPoP Tool

Below are instructions for completing the TPoP tool. Some fields intentionally appear both in Table 2 and Table 3 to provide both a summary and details.

Summary Information (Table 1)

Many types of stakeholders can author a TPoP. However, too many suggested policies presented to a single policymaker might overwhelm decision-making. This might also create the impression of a lack of consensus among researchers or funders. While a diverse authorship group may be ideal, it is more important to release a fully completed TPoP early with a single author or preferably a small group. Depending on circumstances, a successful TPoP authorship team should ideally include:

- Authors with scientific expertise who are both part of, as well as outside of, studies driving the creation or revision of the TPoP
- Community members, leaders, and health and implementation experts in the affected geographies
- Those with experience both authoring TPoPs and using them to successfully influence policy
- Those with experience in regulatory affairs, advocacy, policy, and strategy.

It is helpful to make a TPoP under consideration widely available to the citizens it may affect while also clearly establishing the document's ownership. Fragmented or uncertain ownership will devalue the impact of a TPoP quickly. The best way to make ownership clear is to publish on a platform that affiliates a digital object identifier (DOI) with the specific version of the TPoP.

The modification of a TPoP is just as important. If the authors or owners of a TPoP cannot update it with the most recent evidence, its credibility will suffer. A TPoP will only go so far before it needs a refresh. The speed of new evidence and the breadth of topics in a TPoP can make a refresh exercise a considerable time investment.

Table 6 categorizes types of policies with examples of factors that might prompt a new policy. In this framework, any research study could provide evidence that strengthens or weakens an existing policy. If a research study is going to impact policy, it is necessary but not sufficient that someone is making a clear link from study to policy action. This can be done by completing a TPoP. This should happen at the earliest possible time, ideally in the design phase of a study or before.

Table 6. Describing or Characterizing Policies

Type of Policy	Owner/ provider/ guidance level	Example of a current policy	Example of drivers to a policy change
Top-level, overarching policy	WHO (i.e., Global or super-regional)	Control of soil-transmitted helminths (STH), owned and provided by WHO via guidance, tied to a World Health Assembly resolution. Includes mass drug administration, specific medicines, evidence of specific at-risk populations, sanitation measures, and more.	A vaccine approach to STH. Current thinking is that sanitation improvements or drug availability will reach critical mass before a vaccine could be developed and distributed. A policy introducing a vaccine would be a major change.
One part or component of the overarching policy, sub-policy	WHO (I.e., Global or super-regional)	Mass drug administration today: WHO recommended medicines – albendazole (400 mg) and mebendazole (500 mg) – are effective, inexpensive, and distributable by teachers in schools. The medicine ivermectin (e.g., for *S. stercoralis*) is not yet available at affordable cost.	Identification of a new drug that has a stronger safety record than WHO recommended medicines is unlikely, but if a new medicine was found to be approaching zero cost or much more effective, one could argue to recommend a different drug.
Country-specific	Ministry of Health, Central Government	Egypt maintains regular deworming campaigns (the 3rd in 2017 with WHO and UNICEF) and has distributed 14M tablets of mebendazole.	Nigeria does not fund or mandate an ongoing teacher-based distribution of WHO-recommended medicine. Introducing such a program in Nigeria would be a new policy.

TPoP Template Tool (Table 2)

Indication, disease, condition (Row 1)

As discussed earlier, there are benefits to aligning the TPP with the TPoP. Both documents share "indication (disease / condition)" as their first line item. This section should state the disease or condition for which the intervention is designed. The TPoP is flexible enough to accommodate interventions as varied as nutrition supplements, devices and technology, vaccines and other drugs, or approaches yet to be invented.

Target population (Row 2)

The target population is the group of individuals who need or may benefit from a treatment. The population should be described with characteristics including age range, sex, and frequent comorbidities. Additional characteristics could include gender, risk factors, geographic location, and more. The definition may mention exclusions from that population to clarify the boundaries.

It is critical to invest time describing how different stakeholders may define the target population differently. For example, COVID-19 clearly affected subpopulations differently, and the target population did not extend to all ages and comorbidities. The differences in definitions of the COVID-19 target population may have contributed to vaccine hesitancy. Since the TPoP should make transparent different motivations for target population definition, it is crucial that this section provides multiple definitions.

Commercial players may have defined a broad target population in their TPP for business reasons. The WHO may have defined a more vulnerable target population in their Preferred Product Characteristics document. Meanwhile, specific researchers may have defined a target population for their particular clinical trial design. Trial participants might seek a definition that helps them and their loved ones. By

listing multiple target population definitions, the TPoP can bring stakeholders into a productive discussion on a single definition. Alternately, the discussion can draw out potential risks of using target population definitions that do not follow fact.

Intervention, product, dose (Row 3)

The intervention, product, dose section is the one most likely to match a TPP. This section will likely list brand names of medicines or diagnostics with dose ranges. Since SOC interventions are more established, this section should include the most widely dispensed interventions and their most common doses, by population. The intervention's basic mechanism of action and formulation should also be given.

Usually, the newly proposed intervention will be mature enough that there will be a medicine or diagnostic manufacturer to cite. There may be competing mechanisms of action in a family of similar new interventions, or competing manufacturer products in the same intervention class. In those cases, it is important to list all realistic candidates and their differentiating attributes. This can make clear to policy participants that a decision will need to be made if there is a need for a single solution.

Delivery strategy for intervention (Row 4)

This should cover the delivery strategies for both the SOC and for the intervention proposed as part of a new policy. The delivery strategy is documented to inform discussions about strengths and weaknesses typical for that strategy, not that specific condition. For example, if the delivery strategy is a vaccine with multiple boosters and part of an existing children's health program, this will elicit concerns that need to be sorted, as well as benefits. If the intervention is a device sold in small local pharmacies, that will prompt a different set of concerns and benefits. Lastly, if the new intervention has a different strategy than the SOC, stakeholders will need to come together to align on the approach.

The delivery strategy for an intervention should surface issues for discussion. These may include:

- Identifying sub-populations that would require different strategies than the primary approach
- Differences in delivery strategy, within what is allowed on-label (if a medicine), that have occurred across geographies
- Identifying soon to be available novel medicines or delivery strategies that could disrupt current approaches
- Delivery issues or weaknesses that have come up in locations piloting a new intervention
- Any limits to the delivery strategy in low- and middle-income countries that would need to be addressed by a new policy.

Efficacy, effectiveness (Row 5)

Efficacy and effectiveness are particularly important forms of evidence. Along with early and consistent engagement with policymakers, they are almost always needed for a policy change. Efficacy refers to the performance of an intervention tested in a defined homogeneous participant population under controlled study conditions. This is evaluated in a Phase II trial. Effectiveness refers to the performance of an intervention in a larger and more heterogeneous population in real world conditions.

Policymakers and their technical advisors will likely expect this section of a TPoP to review efficacy and effectiveness studies, along with other relevant research. Essentially, this audience is looking for

evidence that the proposed intervention works well (WHO 2021). They may particularly favor systematic reviews here. These reviews capture a breadth of well-designed studies (e.g., those that use common endpoints, randomized control format, etc.). This mitigates the risk that a single study has undue influence. If a TPoP uncovers a need for additional efficacy or effectiveness evidence, these studies should be designed for inclusion in future systematic reviews.

Policymakers and their technical advisors also expect to understand the pipeline and timeline of future evidence. This should be briefly outlined in this section. TPoP authors should pay attention to the capacity of the policymakers and their advisors to absorb the evidence, ask the best questions, and factor the evidence into decisions.

Fairness, equity, acceptability (Row 6)

Equity and fairness relate to both the potential impact of the proposed intervention and the preexisting health inequities in the target population. Intervention policies can be used to target a health inequity. For example, a policy may improve intervention access in marginalized populations. On the contrary, a policy may inadvertently worsen inequities, particularly if disadvantaged groups are not identified up front (Eslava-Schmalbach, et al. 2017).

Many factors may underlie health inequities. Consider sex, socioeconomic status, age, race or ethnicity, and refugee status. More factors are cited in the Ethics, Equity, Feasibility, Acceptability Framework developed for vaccine program recommendations (Ismail, et al. 2020). It is important to show policymakers that these factors have been considered and that any disadvantaged subpopulations have been identified. This section should also outline how the policy will target health inequities and forecast possible inequitable impact (Alonso-Coello, et al. 2016).

Acceptability refers to the willingness to adopt the intervention. It is important to consider all parties involved: citizens, patients, families, leaders, and influencers. Local social attitudes and religious beliefs may affect willingness. Community trust in healthcare systems and knowledge of the intervention's risks and benefits may also play a role. Even disenfranchised groups may have power to influence policy change if they believe an intervention is unacceptable. Include in the TPoP any groups, tribes, races, or religions who might object to the new intervention. Share potential methods of public dissemination, coordination, and collaboration that could help.

Other considerations (Row 7)

This section may be used for key considerations not captured elsewhere in the TPoP. For example, authors may note how an intervention's use varies by geography or care setting.

Safety (Row 8)

Considerations of patient and citizen safety are a key focus of regulatory reviews. Policymakers may also need to account for links between safety concerns and equity or political factors. Transparency in the specifics of safety can help prevent surprising or damaging policy results. The details of the safety data provided, and its effect on policymakers, will vary by TPoP.

Authors should use this section to summarize adverse events and other safety evidence, including subpopulations with special safety considerations. Relative versus absolute safety is an important distinction. No intervention will be perfectly, universally safe. A policymaker will make a risk-benefit

comparison for the intervention or policy in isolation. Further, the policymaker will compare it to safety data or perceptions of historical interventions, current SOC, and perceptions of other coming interventions. Data that can make these comparisons more concrete can speed up policymaking.

Implementation (Row 9)

"Evidence of the effectiveness of an intervention is not sufficient to produce better health outcomes; barriers and facilitators to its implementation must also be identified" (Hanney, et al. 2003). For this section of the TPoP, a sample of topics to consider when assessing the scale-up needed for successful implementation includes:

- Context
- Costs of scale-up
- Delivery system
- General scale-up and implementation
- Intervention adaptability
- Intervention reach & acceptability
- Monitoring & evaluation
- Sustainability
- Workforce (Milat, et al. 2020)

Attempts to scale-up evidence-based interventions in low resource settings may face any of six common pitfalls (Zomahoun, et al. 2019):

- Cost effectiveness pitfall: accurate cost-effectiveness estimates about real-world implementation are almost impossible, making predictions of economies of scale unreliable
- Health inequities pitfall: some people will be left out and therefore not benefit from the intervention
- Scaled harm pitfall: the harms as well as the benefits may be increased by the scaling-up
- Ethical pitfall: informed consent may be challenging on a large scale
- Top-down pitfall: when scale-up is directed from the top, the needs, preferences, and culture of end-users may be forgotten
- Contextual pitfall: it may not be possible to adapt the interventions to every context

Implementing new policies that include an innovation is challenging. For example, there may be skepticism toward innovations imported from the global North. A clear implementation plan can help address this and other contextual concerns.

Feasibility, practicality (Row 10)

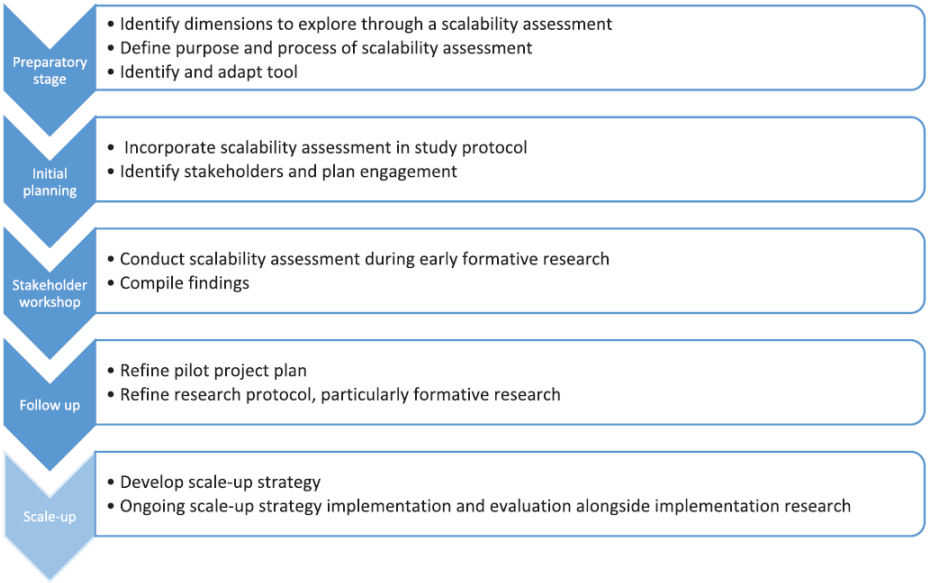
The clinical, social, and infrastructure context in low resource settings must be considered. What might be practical in the global North may not work in other regions. The feasibility of an intervention in varied contexts is key. Some settings may benefit from trained, skilled, and experienced talent. Some may struggle with reliable electricity, internet and supply chains. Consistent, well-managed public health programs may not always be in place.

One study ranked factors associated with implementing the results of an HTA and changing policy. They found that beyond "acceptance of the value of an HTA", the most important factor was the "practicality

of the HTA evidence" (Liu, et al. 2018). Among the attributes listed in 10 frameworks for low resource setting intervention scale-up, "simplicity or ease of adoption" was the most frequently listed. In fact, it was more commonly cited than cost or capacity (Zamboni, et al. 2019).

Assessing practicality requires research into the local environments in question. Communication with local stakeholders is critical. Listing here large obstacles or benefits to feasibility, and any published feasibility studies, will catalyze necessary discussion. Zamboni et al. propose that a better approach to generating data on practicality is to include a scale-up assessment as part of the clinical study itself. This would then extend to a pilot study. Their model is shown in Figure 2.

Figure 2. A Scalability Assessment Process



From "Assessing scalability of an intervention: why, how and who?" by Zamboni et al (2019); reproduced with permission.

Guidelines, Standard of Care (SOC) (Row 11)

Formal, evidence-based health guidelines enable physicians to identify consensus best practice treatments for specific conditions. Health guidelines are less mature and prevalent in low resource settings than in the global North. In fact, physicians in many regions cannot always access guidance databases or documents based on local evidence and practices. At a less local level, health guidelines likely exist (English, et al. 2017). Often, WHO establishes these guidelines. Existing guidelines should be summarized and referenced in this section of the TPoP.

Standards of care could be adopted from global policy through policy transfer. They could also result from existing or new national policy. Or, they could form organically in health centers across a country. In a TPoP, documenting the specifics of both current and proposed SOC is a good way to be clear about the resulting change in practice of the target policy. In short: there is a current SOC, new research emerges with a target policy, and if the advocacy effort and intervention are effective, the new intervention is introduced as the intended SOC.

Policymaker engagement (Row 12)

Early, consistent engagement with policymakers before, during and after the clinical research is the top factor predicting when research shapes policy change. "On whether evidence was used in policy: the quality of the relationship and collaboration between researchers and policymakers was determined to be the single most mentioned facilitator" (McCaul, et al. 2018)**.** Further,

> *"Researchers need to spend time getting to know policy and practice organizations and need to give up some control over their research. Giving up control in this way requires a greater tolerance for uncertainty, but the payoff is frequently better engagement, more immediate effects of the research, and sustained engagement"* (Theobald, et al. 2018)*.*

Each discussion with a policymaker is an opportunity that can move the policymaker forward to a decision on policy change. While some researchers might have experience engaging with policymakers, it is more common that they are not familiar with the policy interface. Having a tool in hand to support discussion is crucial. The TPoP might be most valuable as a discovery tool with policymakers to understand what is needed to inform their decisions. This section of the TPoP should summarize policymakers' views on both the current and proposed policies. It should also give dates of important policymaker engagements and the outcome of those discussions.

Communication and convenings (Row 13)

Policymakers will have interest in whether key opinion leaders have reviewed the potential new policy. In this situation, those key opinion leaders will include local experts, local researchers, members of public health services and hospitals, technical and expert advisors, physicians, significant community representatives, and academics. Policymakers will want to understand whether those parties have been able to talk through the costs, benefits, opportunities, and challenges of the intervention. Further, they will look at whether any consensus has been reached. These are important areas of communication to summarize in this section of the TPoP.

Policymakers may also rely on credible advocacy and support from experts known to their populations. Here, convenings can be helpful. They can help a policymaker feel comfortable that all parties have had opportunities to voice objections and assimilate knowledge. One study found:

> "…organizations vulnerable to assessment…might need to need to draw on expert knowledge to meet expectations about organizational legitimacy or appropriate policymaking…those dependent on technical appraisals will be keen to signal their expertise to underpin the legitimacy of their organization, or to substantiate decisions made." (Boswell 2017)

Beyond convenings, communication with policymakers is as much an art as a science. From one researcher interviewing policymakers in Africa: "policymakers stated that research utilization is already a lengthy and time-consuming process. 'Usually, I do not have the time,' (participant #18). Even if research is considered important, it still requires a significant amount of time to search, locate, access, and review the relevant literature. 'It demands sacrifice" (participant #11)'" (Albert, Fretheim and Maiga 2007). Dissemination must be tailored to the individuals with influence. "Too often the experience of research is to find long reports consigned to dusty shelves in government and donor offices" (Esnor, Clapham and Prasai 2009).

Standardized tools like the TPoP can help the process be more like science than art. When using tools or engaging global guidance bodies, it is important that relevant experts who may have a conflict of interest are still able to participate in discussions. There are ways to ensure those convenings can include non-voting experts.

The use of expert bodies for clinical practice guidance can be helpful as new policies are being considered, as well as after adoption. Organizations like the UK's National Institute for Health and Care Excellence, the WHO Evidence-Informed Policy Network, and the WHO's Global Clinical Practice Network all have global reach and influence.

Political factors (Row 14)

Nearly all systematic reviews of factors affecting whether research will influence or make new health policy include politics. A TPoP can gently make political context and influences transparent to all stakeholders. This lessens the relative power of political factors. It can also help stakeholders craft solutions that allow intervention success to live alongside political realities. Variables affecting political factors will differ by geography, nation, disease being addressed, type of intervention, and whether policy is being decided at multi-national levels such as assemblies, agencies or working groups. This section should describe the key political factors relevant to the intervention and policy in question.

Costs, affordability (Row 15)

Costs are a critical factor in deciding how to change health policy. Before estimating the costs (or savings) of scaling up a new intervention, it is necessary to identify specific costs and related factors. In low resource settings, cost questions may touch on contextual issues that may not seem tied to healthcare. In conversations with policymakers, embracing non-traditional cost questions is likely to be helpful. Questions identified from real-world policy cost conversations to consider summarizing in the TPoP include:

- Is a donor or foreign government paying for the new intervention, and if so, for how long will that support last?
- Will a government be paying for the new intervention, and if so, what is the cost and which department's budget will it come from? Is it affordable and does it represent value for money? What will be the impact of spending money on this rather than something else?
- What costs will the patients, citizens, or consumers bear?
- What will the scale-up, implementation and changeover costs be? Including any changes in health care delivery, will there be long-term savings?
- Who is benefiting financially from the new investments (e.g., a pharma, device manufacturer, other)?
- Do these incremental costs affect our relationships with non-state actors, and if so, how?
- Are there are cost-sharing potentials or other schemes to defray costs?
- Are nations offering heavily discounted but potentially less effective alternatives?
- Are there unforeseen costs?

TPoP Template Case for Change (Table 3)

Executive summary structure

An introductory case for change TPoP could follow the format shown below and use the information gathered in the corresponding template:

A Case for Change: ___ [name of new policy] ___

Desired change in policy

- Our __ [population]___ suffers from ___[indication]___ leading to ___ [health effects] ___.
- We propose that ___ [sovereignty] ___ introduce ___ [policy] ___ leading to __ [briefest summary benefits] ___.
- This policy could be implemented by ___[time]___, require an investment of ___[amount]___ and partnership with ___ [required or proposed parties for implementation or investment]___.

Current policy, current state

- Our current policy for ___ [indication, condition] ___ is ___[policy]___.
- This policy has been in place ___[duration]___ and has ___ [insert benefits to date] ___.
- Unfortunately, this policy ___ [differences from proposed policy] ___, and the current policy ___ [negatives, costs, or limits of current policy, unrelated to proposed policy] ___.

Benefits of new policy

- The new policy could lead to ___ [insert number of lives saved or quantitative benefit] ___ vs. our current policy.
- Further, the new policy would ___ [insert new secondary health benefit vs. current policy] ___.
- The new policy would ___ [insert new non-health benefits vs. current policy, including financial benefits if any] ___.

Approaches to achieve new policy, and tools

- This new policy's implementation could be implemented ___ [summary of approach] ___.
- The approach is practical due to ___ [attributes of the implementation] ___.
- Tools at hand include ___ [mention of HTA, previous implementations elsewhere, other tools available] ___.

Additional evidence needed if any

- Existing evidence is _____ [insert study outcomes & evidence] __.
- Current gaps to required evidence includes _____ [insert unanswered questions answerable by research] _____.
- Those gaps could be closed by conducting the following___ [insert studies or other exercises if studies not appropriate] __.

This format has the benefits of an executive summary. It conveys enough information to hold discussions with those unlikely to study the details or read further. It would be followed by the body of the TPoP Tool (**Table 2**).

Additional background and instruction is given below for the last two rows of the Case for Change (Table 3).

Existing use of the proposed policy (Row 22)

Policy agendas may be adopted from an international level to a national level, or between nations, in a process called policy transfer. Dynamics in policy transfer include influence, pressure, and negotiation. Major health concerns in low resource settings can be supported by international governance and donor organizations. Results from a 2017 landscape analysis of global health policy transfer are shown in Table 7: the relative frequency of policy transfer, with the entity originating the policy, the country adopting the policy, and the topic and type of actors involved (Jensen, McPake and Jones 2017).

Table 7. Healthy Policy Transfer as Mechanism for Changing Health Policy (Jensen, McPake and Jones 2017)

Origin countries		**Recipient countries**		**Types and programmes of health system change**		**Categories of 'policy-maker'**	
Global policy networks	51	Other African countries	30	HIV/AIDS	16	International agencies	53
United States	12	Other Latin American countries	16	Sexual and reproductive health	13	National elites	41
Other African countries	7	Other Asian countries	21	Efficiency and equity in health systems	10	Civic organisations	23
Other European countries	4	Other European countries	11	Access to medical care	9	NGOs	18
Other Asian countries	3	South Africa	9	Vaccination and immunisation	6	Health professionals	13
South Africa	3	India	6	Population	5	Government ministries	11
United Kingdon	2	Zambia	6	Drug enforcement	4	Private sector	10
Brazil	1	Malawi	5	Health insurance	3	Academics	
		Kenya	4	Case management of childhood illness	2	Local communities	6
		Bangladesh	3	Disease preparedness	2	Civic leaders	5
		Brazil	3	Malaria	2	Political parties	4
		Burkina Faso	3	Mental health	2	Media	1
		Mozambique	3	Use of aid in health services	2		
		Pakistan	3	Nutrition	1		
		Thailand	3	Tuberculosis	1		
		Zimbabwe	3	Urban-rural health worker relocation	1		
		Global policy networks	1				

Policy transfer introduces the questions: for any intervention, will the standard or adopted policy for any region or nation originate from the WHO? If so, should engagement with policymakers happen in Geneva? Should they happen in the low resource setting country and ministry of health?

When policy transfer is the source of the proposed policy change, include in the TPoP the origin country, recipient countries, program type, and policymakers for the new policy. Consider including a secondary tier for each of those categories if needed. List countries that have already adopted the intervention. Then, include any printed or anecdotal evidence of their success or failure. Ideally, reach out to officials from that country to learn more.

Minimum Policy-Important Difference (MPID) (Row 23)

Effective policy, and effective policy change, will be measurable. Its effectiveness should be quantitatively measurable. The change in effect should be "valuable enough to be worth doing" or "makes a difference" or "matters significantly to the community / society" (Polisene, et al. 2020). Such statements establish whether and how a proposed change will be significantly superior to the status quo or at least non-inferior to it.

Like the Minimum Clinically Important Difference in clinical trials (Copay, et al. 2007), the MPID can be thought of as the smallest value that is both detectable and meriting policy change. It is greater than the measurement error of a specific population exposure. A difference smaller than the MPID value is not likely to be important and would therefore not justify policy change. The TPoP encourages key stakeholders to jointly set forth one or more MPID value-points. These could be economic value added, Disability-adjusted life years (DALYs) averted, or employment rate improvement.

Example thresholds for policy level endorsement of an intervention's cost-effectiveness include:

- An incremental cost-effectiveness ratio of less than €50,000/DALY averted in high income countries or less than €500/DALY averted or per quality-adjusted life year (QALY) gained in low resourced countries. For example, Medicare in the US has used coverage thresholds around $50K/QALY for more than 20 years, and commercial insurers do as well. The same is true for other HTA committees who make policy or coverage decisions in their respective jurisdictions.
- Less than 25% of per capita annual health services spend may be approved and sustainable for a new intervention directed to a life-threatening indication in a low resource setting.

The MPID requires savings compared to total costs of care. It reflects the impact of the health condition on patients, their caregivers, and the economy. It also captures societal issues, including development goals, gross domestic product, costs of care, and opportunity cost. MPID decision-making should consider whether allocating resources to one group of patients will indirectly harm others. This make take the form of diverting resources away from other priorities, or consuming resources such that other needs are left unaddressed.

When completing the TPoP section on MPID, consider one of two approaches. A detailed approach would include adding an econometrician or policy modeler to the author team and completing a detailed analysis. A more basic approach would consist of trying to understand a level of benefit from the intervention that is so low that the costs to initiate it as the new SOC would outweigh the benefits. Then, identify if there is evidence or arguments to show the benefit of the intervention exceeds those costs.

Items Not Addressed Here

This in-depth TPoP information has limited scope, and so leaves some topics unanswered. The TPoP authors should make their best efforts when deciding how to define and use their TPoP. Topics that the TPoP template and this information do not address include:

- How far should policy reach and how customized does it need to be per country or population?
- Should there be versions of a TPoP customized for varieties of interventions, such as vaccines, nutritional interventions, or unregistered products?
- Per audience group, what is the engagement plan, and what is the rationale for that engagement plan?
- How meaningful is the TPoP if it does not include individuals from the WHO as audience or authors?

Conclusion

The TPoP is a useful tool to lay out proposed changes to policy and their effects. It can serve as a tool to engage policymakers as well as global health stakeholders. The TPoP can also act as a tool to assist in review and funding of research proposals. With TPoP information laid out on a few pages, most policymakers can easily gauge their sense of risk and impact. A full range of appropriate stakeholders can both add to the content as well as act as an audience. Required thresholds for research outcomes to change policy should be identified in the TPoP-framed discussion.

Assembling publicly available data into a TPoP takes time and subject matter expertise. To a clinical researcher specializing in studies for new life-saving discoveries, the concept of producing a TPoP might seem intimidating or unfulfilling. However, it provides an opportunity for broader engagement and input.

The global health community can play a role in making policy decisions more transparent, global, granular, and quick. Global health community members could use a standard TPoP as one tool in that effort. Imagine if all evidence was presented to policymakers in the same format. Such cohesiveness from funder, researcher, and other presenting communities could lead to a faster policymaker response.

Funders, sponsors, and stakeholders should be asking new questions. How does this clinical study fit into a policy goal? Is the research designed to meet a specific policy or public health goal? Has engagement with policymakers taken place in designing the study? If successful, how will that change in policy proceed? Does the principal investigator or grantee understand how to excel at the interface of research and policy? How can funders or grantees invest in additional capabilities to collect data to populate a TPoP, develop a strategy for advocacy and dissemination, and push beyond defining new evidence? Should researchers be engaging policymakers before a study begins? Should the policymakers' questions define the research questions to be answered?

Both a hands-on tool populated with current data, and a method to frame discussion, a TPoP can act as a beacon for researchers, funders and other stakeholders to thrive at the interface of evidence generation and policy.

Appendix A: Example Target Policy Profile

The following information was added solely to provide an example of a completed TPoP and does not or may not represent the opinions of The Bill & Melinda Gates Foundation and does not represent clinical nor policy recommendations.

October 2022

Table 1. Target Policy Profile Template **Summary** Information

Target Policy Name:	Single Dose HPV Vaccine Program
High level policy currently in place (if applicable):	Two doses of vaccine in 9-14 years old (y)
Target audience	WHO SAGE
Key stakeholders:	WHO SAGE and Ministries of Health / EPI Program
Authors:	PATH
Consulted parties:	The Single-dose Consortium, March 2021
Date of Last Revision:	Updated by Megan Wysong, MPH, with some additions from Doug McNair, October 2022

Table 2. Target Policy Profile Template **Tool**

		Target Policy 1-Dose Regimen	**Current Policy/ SOC 2- or more Dose Regimen**	**Pros/ Cons of New Policy**
1	**Indication, disease, condition**	Vaccination against human papillomavirus (HPV) is recommended to prevent HPV infections and HPV-associated diseases, including cancer. This policy focuses on shifting from two-dose to single-dose HPV vaccination for girls 9-14y, one or two doses for young women 15 – 20y and two doses with a 6-month interval for women older than 21 years.	Currently it is recommended by WHO to have a 2-dose regimen for girls under 15y and 3-doses for girls and women over 15y. In the United States, the Advisory Committee on Immunization Practices recommended routine 2-dose vaccination at age 11 or 12 years for girls since 2006 and for boys since 2011.[1]	Single dose will be more cost effective, and its impact likely greater than 2 doses because of increased coverage, ease of delivery, and reduction in cost of the vaccine.
2	**Target population**	Ideally an HPV vaccine is given prior to HPV exposure and sexual initiation. It is recommended to give a single dose to girls between 9 – 14 years of age.	In October 2016, the Advisory Committee on immunization Practices (ACIP) recommended, two doses given to girls aged 9-14y except for people known to be immunocompromised or with HIV infection.[2]	In both scenarios, the primary target age range is 9 – 14-year-old girls. Catch-up vaccination is recommended for all girls and women up to the age of 26 years.
3	**Intervention, product, dose**	Three HPV vaccines are licensed for use in the United States: Bivalent HPV vaccine (2vHPV, Cervarix, GlaxoSmithKline) introduced in 2009, quadrivalent (4vHPV, Gardasil, Merck) introduced in 2006, or 9-valent (9vHPV, Gardasil 9, Merck) introduced in 2014.	Initially the vaccine was licensed to be administered in 3-doses. Research since 2006 has reduced the worldwide vaccination policy to 2 doses. Bivalent, quadrivalent, and 9-valent vaccines have been used for multi-dose formats. Most cancers are caused by HPV 16 and 18 which are targeted by all three vaccines. The 4vHPV also targets HPV 6 and 11. The 9vHPV also protects against HPV 31, 33, 45, 52, and 58.	All three vaccines have been shown to be effective in either 1-, 2-, or 3-dose regimens. One of the cons for the new single dose policy would be that some girls could be missed if they were not at school on the day of vaccination.

		Target Policy 1-Dose Regimen	Current Policy/ SOC 2- or more Dose Regimen	Pros/ Cons of New Policy
		Additional vaccines are in the process of being licensed in China and India. This does not change for the 1-dose regimen.		
4	**Delivery strategy for intervention**	The envisioned settings would not change for 1-dose regimen. These settings include school-based delivery or using public or private clinicians in high-income countries using either an opportunistic or organized delivery strategy. In low resource settings, annual vaccination campaigns, school- and clinic-based delivery would be appropriate. Routinizing the delivery with other vaccines would reduce costs for delivery.	The 2-dose regimen is currently administered in school and / or clinics targeting 9-14-y girls. Currently, in high income countries, vaccination is either organized or opportunistic. Many countries use school-based delivery or delivery through public or private sector clinicians, pediatricians, general practitioners, or gynecologists. Some countries co-administer HPV with Hepatitis B vaccination.[3] In low- and middle-income countries, the vaccination setting includes annual vaccination campaigns, school-based for enrolled girls and clinic or community-based administration for girls not in school.	Delivery methods could change with a single dose formulation making it more cost effective and more in line with national immunization programs. By using routine systems, delivery costs could be saved. School-based administration is hampered by absenteeism, difficulty in determining age, and complications of a grade-based approach but still yields the highest coverage.[4]
5	**Efficacy, effectiveness**	Women who have received 1- or 2- doses had similar efficacy against persistent HPV infection over 4 years[5] and 9 years[6] of follow-up. In the CVT study, antibodies in all subjects were lower than a multi-dose regimen and persist at levels several-fold above natural infection up to 11 years after a single dose[7]. Immunobridging from the DoRIS study to CVT and IARC India study, found HPV 16 and 18 non-inferior comparing 9 – 14y girls to those in adult women who received 1-dose.[8] These results show that a single dose of HPV vaccine induces immune responses that are comparable in different populations and geographic contexts.[9] Additional RCTs are underway with results expected between 2022 – 2029. Key endpoints include humoral and cellular immunogenicity, cost-effectiveness, acceptability, immunobridging, population effectiveness, cross-protection, herd protection, impact of HIV, vaccine efficacy, and durability of protection.	Prelicensure HPV vaccine efficacy trials found high efficacy against infection among vaccinees who received 2-doses and those who received 3-doses.[10] Post licensure effectiveness studies have found lower effectiveness against various HPV-associated outcomes among vaccinees who received 2-doses compared with those who received 3-doses.[11] Human papillomavirus antibody responses to the 9vHPV vaccine among girls and boys (aged 9 – 14y) receiving 2-dose regimens were non inferior to a 3-dose regimen in young women (aged 16-26y) after last vaccination.[12] Six additional studies found similar results for 4vHPV and 2vHPV with immunogenicity found to be noninferior with 2-doses in persons aged 9 through 14 compared with 3-doses in a group in which clinical efficacy was demonstrated.[13]	There was similar efficacy and effectiveness between 1-dose and 2-dose except for a small decrease in immune response with 1-dose.[14] Due to high drop-out rate between first and second dose in real world implementation, 1-dose is being implemented in many countries involuntarily by virtue of girls not returning for the 2nd dose. Within low and middle-income countries, there is suboptimal coverage of the 2-dose schedule (<15y it is only 13% worldwide and only 8% in low- and middle-income countries).[15]

		Target Policy 1-Dose Regimen	Current Policy/ SOC 2- or more Dose Regimen	Pros/ Cons of New Policy
6	**Fairness, equity, acceptability**	This would be a global policy benefiting all countries and all populations. Reduction in the per person cost of vaccination could facilitate expanded population coverage in those countries with the lowest coverage rates, which could provide a realistic pathway. Reducing global disparities in HPV infection and cancer prevalence.[16]	A study in Kenya found that Kenyan women knew very little about cervical cancer or HPV vaccination however they were willing to have their daughters vaccinated with a vaccine that would prevent cervical cancer with preference for an inexpensive vaccine requiring fewer doses.[17] A systemic review of peer-reviewed studies on knowledge and awareness of HPV and HPV vaccine and willingness and acceptability to vaccinate found high levels of willingness and acceptability but low levels of knowledge and awareness among GAVI eligible countries in Sub-Saharan Africa.[18]	While 2-dose implementation is recommended it is inaccessible to low-income and lower-middle-income countries due to cost and supply constraints limiting scale-up. Less than 5% of eligible girls in low- and middle-income countries have received the HPV vaccine, even though low- and middle-income countries account for ~90% of the cases of cervical cancer worldwide.[19] Waiting until all evidence is in for 1-dose could further exacerbate the global disparity. This scenario would privilege individual gains within countries rather than relative gains between and among countries.[20]
7	**Other considerations**	With less doses per person, expansion of HPV vaccination programs could include national scale-up, broader age targets, multiple delivery systems, gender-neutral programs, and potentially vaccination in childhood.[21]	High rate of HIV infections in some countries, high rate of malaria, HPV exposure (increasing with age) may affect vaccine effect. Almost 1/3 of the 107 countries that vaccinate have also started vaccinating boys. This was suspended due to vaccine supply shortages.[22]	The need for a well-organized, nationwide platform of administration, coordinating the administration to all patients, education of health care workers and the vaccine recipients, and the financial means for the vaccine are critical and easier to achieve with single dose.[23]
8	**Safety**	With single dose vaccination programs, there is an expected decrease in rate of adverse events following vaccination. In the DoRIS Study, at 24 months of follow-up, safety was assessed. Only 53 serious adverse events were experienced by 42 of 930 (4.5%) of girls, with the most common of which was hospital admission for malaria. One girl died of malaria. Number of events were similar between groups receiving 1-, 2- or 3-doses and no SAEs were considered related to vaccination.[24]	Prior to HPV vaccine licensure, the HPV vaccines were trialed in 60,000 women and assessed as safe within the statistical constraints of the trials to detect very rare events. Post-licensure surveillance is ongoing, but the vaccine has been determined to be safe, effective, and of great importance to women's health.[25]	Adverse events following HPV vaccination are generally non-serious and of short duration. The vaccine can be used in person who are immunocompromised and / or HPV infected. Data on the safety of HPV vaccination of pregnant women are limited so vaccinating pregnant women should be avoided.[26] With single dose administration, it is expected there would be less adverse events reported.
9	**Implementation**	Two-dose implementation learnings are relevant for single dose, only with less barriers including cost. Key implementation changes will need to happen in-country to reflect updates to planning, scheduling	Barriers to uptake include cost (vaccine and delivery cost) and programmatic challenges (novel age of target group, competing new vaccine introduction priorities) and vaccine availability.	Several factors have hampered 2-dose implementation including supply challenges, programmatic challenges, and costs related to delivering 2-doses to those who are not typically part of childhood vaccination

		Target Policy 1-Dose Regimen	Current Policy/ SOC 2- or more Dose Regimen	Pros/ Cons of New Policy
		activities, coordination, standardization of documents, procurement, storage and cold chain, training, social mobilization and communication, vaccination strategies, record-keeping, monitoring, and supervision.[27] In order for WHO's Global Elimination Strategy for cervical cancer prevention and control to be reached countries need to focus on delivering prophylactic HPV vaccination (90% of eligible girls vaccinated), screening for HPV-associated precancer with appropriate follow-up (70% of women screened once in their lifetime) and timely, effective treatment for women found to have invasive cancer, including symptom management and palliative care (90% of women receiving treatment) and reduction in deaths from cervical cancer (30%).[28]	Even with these barriers and challenges, there has been a lot of learning on vaccinating the adolescent age group. A study in South Africa showed overall success in terms of coverage (86% of age-eligible girls reached) with the primary challenges being obtaining informed consent, vulnerabilities in cold chain capacity, onsite management of adverse events, and rumors and misinformation in the community.[29]	programs. Add in the high cost of HPV vaccines, particularly for middle income countries. Implementation materials will need to be updated to reflect the change in policy including documents related to storage and cold chain, training, social mobilization, record keeping, and monitoring. Single dose will also reduce the challenge of tracing girls for their second dose and allows for financial and human resources to be redirected to other health priorities.
10	**Feasibility, practicality**	One dose would allow for simplification of implementation including fewer missed doses, would remove the need for additional visits, reduce delivery costs, and ease integration of single vaccination visits with other school-based interventions (e.g., integrating health education on sexual and reproductive health topics, hand hygiene, and other services). Accelerating the impact using multi-cohort vaccination strategies across a wider initial age range may also be feasible if the vaccine supply is available to support it. Prior to the WHO recommendation, countries could delay a 2nd dose by 2 to 3 years alleviating the supply issue. Once the results of the single-dose trials are available, the 2nd dose could be eliminated.[30]	A study was carried out in Tanzania in 2019, looking at awareness, feasibility, and acceptability among health care workers and community-level stakeholders. The Tanzania HPV 2-dose schedule was well accepted by community stakeholders, there was adequate knowledge of HPV vaccine and the vaccination program by health workers and school personnel. However, continued and sustained technical support for the integration of HPV vaccination as a routine immunization activity and reinforcement of basic knowledge of HPV in specific community groups was needed especially given the time lag between 1st and 2nd dose.[31]	Vaccination programs have been introduced in 80% of high-income countries yet only 41% of low- and middle-income countries had an implementation program as of 2019 leading to a global coverage of only 15%.[32] One dose will be less burdensome on the health care system and health care workers. Two dose is a considerable health care utilization burden in low- and middle-income countries both in terms of girls needing to return to the facility or health care workers having to return to the school for 2nd dose.
11	**Guidelines, Standard of Care (SOC)**	WHO issued a Global Elimination Strategy, aimed at aligning and accelerating efforts to eliminate cervical cancer. The strategy requires countries to vaccinate 90% of the girls by age 15 by 2030. Presently 2-dose coverage is 13%. This strategy could be easier to achieve if 1-dose regimen was in place.	In 2007, the American Cancer Society issued guidelines for HPV vaccine implementation in the United States.[33] These guidelines covered the use of prophylactic HPV vaccines, including who should be vaccinated and at what age, as well as	WHO position paper for single dose is expected in December 2022. This will prompt revision of guidelines and SOC at the global and national level.

		Target Policy 1-Dose Regimen	Current Policy/ SOC 2- or more Dose Regimen	Pros/ Cons of New Policy
		A WHO Position Paper on single dose schedule is expected in Dec 2022. Following the position paper, guidelines will be drafted or revised by various stakeholders including Gavi, American Cancer Society, and individual countries.	summary of policy and implementation issues. Implications for screening were also discussed.[34] The most recent WHO Position Paper on 2-dose HPV vaccination was issued May 2017.[35]	The guidelines for 2-dose regimen have been time-tested and thus will carry more weight than the newly drafted 1-dose regimen.
12	**Policymaker engagement**	Individual members of the Single Dose Consortium Committee were consulted. The WHO working group established and has met twice. Extending the interval between first and second doses was recommended by WHO in 2019 as a stopgap while additional evidence was gathered. The intent behind the lengthened interval was for countries to potentially drop the 2nd dose when evidence showed that it was not necessary. GAVI HPV sub-group has been briefed. National and regional regulatory and vaccine advisory groups have been formed. WHO SAGE recommendation for single dose issued in April 2022.	In 2015 – 2016, the Advisory Committee on Immunization Practices (ACIP) held monthly telephone conferences to review evidence on the immunogenicity, efficacy, post licensure effectiveness of a 2-dose schedule.[36] Based on the evidence, the Committee made recommendations on routine and catch-up age groups, dosing schedules, special populations, contraindications, and interrupted schedules.[37]	The Single Dose Consortium was formed to collate evidence for WHO in support of moving from 2-doses to 1-dose. This Consortium was not actively involved when the decision was made to go from 3-doses to 2-doses. Other bodies, like ACIP, GAVI and other stakeholders are involved in updating guidance and issuing concurrence following the decision to move to 1-dose.
13	**Communication and convenings**	WHO's SAGE met in April 2022 to evaluate the evidence that has emerged for single dose schedules. The SAGE made a recommendation to WHO to move to a 1-dose schedule. New policy could utilize existing community of practice platforms to educate others about policy change. The same people would need to be educated about the vaccination in a single dose scenario as compared to a multi-dose scenario.	Building a community of practice by establishing HPV Council and an HPV symposium could be useful at a national level. At a local level, using influential people, training of health care providers, teachers, pharmacists, and parents is needed. Recent studies have shown stark knowledge gaps about HPV from policymakers to health care workers to parents and teens in both high-income countries and low- and middle-income countries.[38]	Communication channels would not change. Educating the population is essential before initiating or optimizing the immunization programs. Influential individuals like tribal, spiritual, or political leaders can be used to convey the information. Announcements made via newspaper or even through various social media platforms.[39] These methods would only need to be used once a year rather than twice in single dose administration.
14	**Political factors**	In 2018, the Director-General of WHO issued a global call for action to eliminate cervical cancer as a public health problem within the 21st century. A Global Strategy, aimed at aligning and accelerating efforts to eliminate cervical cancer was issued which requires countries to vaccinate 90% of the girls by age 15 by 2030. Presently 2-dose coverage is only 15%.[40]	In 2014, WHO issued a recommendation that National Immunization Programs should adopt a 2-dose schedule of the HPV for children 9 – 14 years of age. In the United States, proposals have been put forth for routine and mandatory HPV vaccination of girls. This has been controversial due to beliefs	WHO Global Elimination Strategy aligns well with single dose strategy reaching more girls with vaccination. To achieve the call to action, it is estimated that 120 million doses would be needed per year after 2025 when supply constraints should subside.[42]

		Target Policy 1-Dose Regimen	Current Policy/ SOC 2- or more Dose Regimen	Pros/ Cons of New Policy
		If the UK or another high-income country implements single dose, it could serve as a model for low- and middle-income countries also choosing to make the switch. These early adopter countries can demonstrate the effects, positives, drawbacks, and resistance experienced with this change in policy. Gavi will be influential on whether countries take up a single dose policy, so it will be important to get Gavi's concurrence on the policy.	that vaccines increase sexual risk taking, mixed messages about abstaining from sexual intercourse, usurps parental authority, and increases the potential for developing health disparities. Those in favor of mandatory vaccination, see the value in administering cost-effective, age-appropriate public health measures targeting a life-threatening problem.[41]	The annual global birth cohort of girls is currently at 60 million, only 10 million of whom are currently being vaccinated, mainly due to lack of HPV vaccine offerings in low- and middle-income countries.[43] With 1-dose, more girls could be offered the vaccine, especially in countries with the highest burden.
15	**Costs, affordability**	A single dose regimen could reduce economic costs by ~30-40% based on decrease of recurrent costs such as number of vaccine doses.[44] Sixty-four million cervical cancer deaths are projected to be avoided in the next 98 years by reducing the recommended regimen from 2- to 1-dose based on dynamic modeling.[45] The introduction of generic HPV vaccines could immediately disrupt the global market, providing access to affordable vaccines for national programs.	HPV is one of the more expensive vaccines in the GAVI portfolio at $4.50/dose with lowest-income countries purchasing HPV vaccine for US $3-$5.18 per dose.[46] The true manufacturing costs are estimated at US$2.07 – 3.05 per dose for the first set manufactured each year, because of high fixed costs, but are at only US$0.48 – 0.59 per dose for a second set.[47] The PAHO Revolving Fund for Access to Vaccines bulk purchasing program has brought down the price of Gardasil to US$10.48 for eligible countries in the Americas.[48] In the United States, it is reported that the cost per dose is roughly $250, which is a significant barrier to overcome without assistance programs.[49]	Costs related to the actual vaccine schedule and ancillary components will decrease with a 1-dose policy. The threshold for cost-effectiveness is 70% coverage, in low-income countries implementing HPV, 41% coverage has been achieved with two dose administration.[50] In the longer term, access to HPV vaccines will improve the development of new, low-cost, and quicker-to-produce HPV vaccines coming onto the market from China and India.

Table 3. Target Policy Profile Template **Case for Change**

	Description of current policy and approach	Policy profile for countries to decide whether to adopt the HPV vaccine single-dose regimen as primary prevention for cervical cancer.
1	**Existing WHO guidelines relevant to target policy**	Per the April 2022 WHO SAGE Meeting, the current recommendation to WHO is for countries to choose between a 1- or 2-dose schedule for girls 9 – 14-year-old. One- or two-dose schedules may be applied for young women aged 15 to 20 years old and 2-doses with a 6-month interval should be used for females older than 21 years. Boys and older males can follow the same dose schedule as females while additional efficacy and immunogenicity (antibody response) data of a single dose schedule is being generated. Immunocompromised individuals 9 years and older should receive 2-doses, though 3-doses would be considered optimal if programmatically feasible.[51] In June 2022, SAGE made the recommendation to WHO to optimize the vaccine schedule in older age cohorts. Those aged 15 – 20 years may receive 1- or 2-doses, while those aged greater or equal to 21 years should receive 2-doses with a 6-month interval.[52]

		A WHO Position Paper on HPV vaccination 1-dose will be revised following a stakeholder consultation by WHO with an expected release in December 2022.
2	**Proposed change**	Shift to a single dose HPV vaccination.
3	**Reason for the change**	A dose-reduction recommendation to a single-dose regimen could have significant programmatic benefits by potentially reducing the costs of vaccine supply and improving global vaccine accessibility and/or delivery. This may be particularly beneficial in the context of the COVID-19 pandemic and in case of vaccine shortages. Different delivery strategies for a single-dose schedule could also contribute to increased accessibility and sustainability of the vaccination programs in both Gavi-eligible and non-Gavi-eligible countries. Reduced costs would also enable a larger number of people to be vaccinated, either in target age ranges and/or catch-up of older adolescents and young women, through an increased number of vaccination programs, with commensurate lower rates of HPV infection and malignancy.
4	**Existing evidence supporting a proposed policy change**	The cost of the HPV vaccine and its delivery in a multi-dose schedule have created barriers to HPV vaccine introduction and program sustainability in low- and middle-income countries. Some observational data and biologically plausible mechanisms exist to suggest that a single dose of HPV vaccine may be sufficient to elicit a protective immune response against incident and persistent HPV infections, which are the necessary prerequisites for further development of cervical lesions and, in the longer term, cervical cancer. From previous studies, 1-dose HPV vaccination induces lower serum antibody titers compared with 2 and 3-doses. Despite inducing significantly lower neutralizing antibodies, a single dose of HPV vaccine induces antibodies that are of similar function (neutralization, avidity) in girls and young women (which appear to persist for a similar duration) compared with 2- and 3-dose vaccine regimens.[53] From various sources, there is reasonable real-world, observational data supporting a single dose schedule. In addition, there is some evidence from the CVT study (study participants with incomplete vaccination schedule having received a single dose) and India-IARC study (study stopped early for non-vaccine related reasons with many subjects having received a single dose) which showed long-lasting protection against infections with HPV 16 and 18 for a single dose.
5	**Benefits of new policy**	The policy would reduce cost and healthcare utilization; lead to increased coverage within existing programs or through expansion of national vaccination programs; an increased likelihood of success for long-term sustainability; herd effect in unvaccinated women and men (HPV induced gender specific malignancies like penile, oropharyngeal, and anal found in males); and greater programmatic ease (e.g., no need for follow-up which is a challenge in low- and middle-income countries. Comparative health impact modeling analysis favors early implementation of a single-dose HPV vaccination schedule ahead of randomized controlled trials (RCTs) which will likely yield greater health benefits than waiting for completion of the trials prior to implementation.[54] There will be greater health benefits providing vaccines to 10 – 14-year-old girls in 2021 and not delaying.[55] By delaying, these girls will age out of vaccination eligibility.[56]
6	**Risks of new policy**	The risk of the policy of a single dose vaccination regimen could be a decrease in protection or duration of protection against cervical cancer. Monitoring of effectiveness will be key, as to determine whether a booster might be needed in the future, which could be 10-20 years after initial vaccination.
7	**Limitations of existing evidence**	Most of the evidence from clinical trials or observational studies comes from comparisons made between clinical trial participants who completed or failed to complete standard 2- or 3-dose vaccination schedule. Some of the limitations of the observation and post-hoc analysis includes lack of randomization, not double-blinded, and possible bias including a high vaccination coverage rate, risk of pre-existing infection, and catch-up programs in 1-dose patients. Formal randomized clinical trials assessing single dose efficacy using clinical outcomes have been initiated. Further, it is known that the quantity, but not the quality, of antibody response is lower with single dose compared to two doses, although the clinical significance of this observation is unknown due to few breakthrough infections following vaccination. The correlate of protection against HPV infection and disease is also unknown. Duration of follow up with single dose evidence so far is up to 7- and 11-years

		post vaccination in observational studies in India-IARC and CVT studies, respectively. Duration of protection beyond the existing trials' timelines will continue to be an uncertainty. Post-hoc analyses of randomized trials have found high effectiveness following a single dose however the interpretation of these analyses is limited by several factors including women with incomplete vaccination schedules not randomized by number of doses, small sample size, and low number of incident or persistent infections.[57] Effectiveness studies can be compromised by biases such as increased likelihood of prior HPV exposure in adult subjects receiving less than the recommended number of doses. To date there has been limited though emerging evidence of HPV effectiveness (direct or overall) on cervical cancer due to the progression of HPV infection to invasive cancer taking approximately 5 – 20 years or longer.
8	**Evidence needed to achieve the policy change**	There is demonstration of efficacy in an adult population. In younger ages, demonstration of immunological non-inferiority to adult population in whom vaccine efficacy has also been demonstrated (post vaccination and at a timepoint ≥2 years post-vaccination). There needs to be additional vaccine effectiveness/ impact studies. Listed are some of the areas needing more evidence: - Demonstration of efficacy of single dose - Evaluation of effectiveness of single dose schedule, particularly in cohorts vaccinated before sexual debut - Immunogenicity data on single dose assessment with immuno-bridging - Evaluation of the durability of protection of single dose Immunobridging data from DoRIS, effectiveness data from the Thailand impact and HOPE trials together with current evidence on single dose should support a WHO policy change. **Durability of protection** Currently, it is not known if a single dose of HPV vaccine will provide a sufficient and durable enough level of efficacy against persistent HPV infections to support a recommendation for a policy change to a single-dose vaccination strategy. This question is being addressed through the CVT trial and continued follow-up of the India study cohort. The IARC - India study will provide robust evidence on the protection offered by a single dose up to 18 years post-vaccination. **Evidence from purpose-designed intervention studies of single-dose HPV vaccine versus no vaccination or multi-dose schedules** The systematic and Cochrane reviews of trials data highlighted a paucity of evidence from RCTs that specifically randomized participants to receive 1 HPV vaccine dose versus either no HPV vaccine dose or multi-dose schedules. Randomized trials will be able to provide more definitive data on whether single-dose HPV vaccination can protect against HPV-persistent infections and provide immuno-bridging data to other trials without efficacy endpoints. Several ongoing trials are investigating the efficacy and/or immune responses and safety of a single dose of HPV vaccine compared to recommended dose regimens or no vaccination. These trials include ESCUDDO in Costa Rica, KEN SHE in Kenya, PRIMAVERA in Costa Rica, IVIHPV1 in Thailand, and HOPE in South Africa. Immunogenicity trials are also underway including DoRIS in Tanzania, HANDS in The Gambia, and a study in the United States funded by MERCK. **Evidence from different populations and using different vaccines** Undertaking multiple, large-scale efficacy and effectiveness studies across numerous countries is challenging, but current studies (including CVT, India, ESCUDDO, KEN SHE, IVIHPV1, HOPE, MERCK) are already being conducted across multiple continents. Immuno-bridging studies will be important to allow conclusions to be drawn about the potential efficacy of a single dose across further populations and age groups. The current prospective studies are working across a wide age range, from 4 to 26 years, and are covering study populations on five continents. While the evidence base to date is largely derived from studies of the bivalent and quadrivalent HPV vaccines, new and ongoing research on single-dose vaccination spans the three widely available commercial vaccines (2vHPV, 4vHPV, and 9vHPV).

		Standardized measurement and reporting of immunogenicity outcomes The inability to compare immune responses of a single-dose HPV vaccine across studies due to heterogeneity in laboratory methods and cut-off thresholds for seropositivity creates a significant gap in evidence. Efforts are now underway to standardize the immunological testing for antibody levels so that the results of the CVT and India trials can be compared directly as well as for future trials (including ESCUDDO, DoRIS, KEN SHE). Antibody avidity indicates the degree of antibody affinity maturation and generally increases over time following encounter with an antigen. Avidity data are available from the CVT and India studies and will be collected in the ESCUDDO and DoRIS trials. Studies are also underway in the DoRIS trial to compare cellular immune responses following 1-, 2-, and 3-doses of HPV vaccines. A systematic review of immunogenicity data among vaccine recipients, stratified by number of doses received was conducted by the Strategic Analysis, Research and Training (START) Center at the University of Washington, but has not yet been published. Once results are available, they will enhance the evidence-base regarding the immunogenicity of single-dose HPV vaccination.
9	**New or upcoming evidence**	A careful review of all data (clinical trials, real-world data, and modelling) has been compiled and will continue to be updated with an assessment of the strength of the evidence. In addition to forthcoming duration of protection data from observational studies (CVT/ India-IARC study), 8 clinical trials are currently ongoing: 1. KEN SHE 2. ESCUDDO 3. DoRIS 4. PRIMAVERA 5. HANDS 6. HOPE 7. IVIHPV1 (Thailand impact study) 8. MERCK Study KEN SHE and ESCUDDO are randomized and will provide good quality data with virologic outcomes for up to 3 years (KEN SHE) and 5 years (ESCUDDO) post vaccination. KEN SHE is scheduled to read out in 2024 and ESCUDDO out in 2025. For KEN SHE, the design is 1-dose at age 15-20 and delayed second dose for 3 years with either 2 or 9 valent vaccine and will report on vaccine efficacy, immunogenicity, cost-effectiveness, persistent infections, and comparison of antibody titers to the DoRIS study. In ESCUDDO girls 12-16 yo are randomized to receive 1- or 2-doses of 2 or 9-valent vaccine and will report on vaccine efficacy, immunogenicity, cost effectiveness, and persistent infections. DoRIS, PRIMAVERA and HANDS will provide immunogenicity data in 9-14yo girls in low- and middle-income countries allowing for immuno-bridging to an adult population in which efficacy has been evaluated. The HOPE trial and the Thailand impact study will provide effectiveness data of a single dose compared to 2 doses. Those studies will be important to low- and middle-income countries evaluating the impact of single dose vaccination at a population level. In addition to these trials in young girls, 1-dose is also being trialed in boys in Tanzania (NCT04953130) and reduced dosing schedule in women who have HIV in Canada (NCT05495906).

		Modeling and health economic data compared no vaccination to 1-dose and showed substantial health benefits and is a good value for money even if efficacy is lower (80-85% vs. 100%) and duration of protection is shorter (10-20 years vs lifelong) than with 2 doses.[58] Impact and cost-effectiveness of adding a second dose is driven by duration of protection and possibly the ability to achieve higher coverage or expand catch up with 1-dose vs. 2- or 3-doses.[59]
10	**Generation of further evidence to fill gaps**	• Efficacy of single dose: KEN SHE and ESCUDDO have been specifically designed to provide evidence of efficacy in prevention of HPV infections after single dose vaccination. Month 18 results from KEN SHE shows that a single dose of Cervarix and Gardasil9 are highly efficacious in preventing incident and persistent HPV infections in African adolescent girls and young women. • Effectiveness of single dose: The HOPE trial and the Thailand impact study (IVIHPV1) will provide effectiveness data of a single dose compared to 2 doses by 2022 – 2024. • Immunogenicity data on single dose: DoRIS, PRIMAVERA and HANDS will generate data after single dose vaccination in the target population and will allow for immuno-bridging to an adult population in which efficacy has been evaluated. Immunogenicity persistence from CVT and India-IARC 1-dose recipients is extended and will provide data for up to 18 years post-vaccination. • Durability of protection: KEN SHE and ESCUDDO will provide data of single dose efficacy up to 3- and 5-years post-vaccination, respectively. • Modeling work will synthesize and integrate new data as they emerge from existing evidence and ongoing studies.
11	**Qualitative health benefits**	It is possible that vaccine acceptance might increase overall with a single dose because willingness to be vaccinated is likely to increase with a "one and done" approach. Furthermore, programs will benefit from not having to follow-up for a second dose. Current coverage of the first dose tends to be much higher than coverage with a second dose.
12	**Quantitative health benefits and cost effectiveness considerations**	Single dose will inevitably be cost saving compared to multi-dose. In addition, single dose could lead to higher coverage rates, so the health benefit is likely to even increase. Cost of course will be less, not only due to reduced vaccine cost, but also reduced delivery costs.
13	**Target countries**	This policy change would have significance for all countries. As of Mar 2022, 117 countries have introduced the HPV vaccine in their national immunization programs, representing only one-third of the global population of girls and 40% of the global burden of cervical cancer.[60] Single dose administration will likely be easier to implement and could be incorporated into existing immunization programs. Expected early adopter countries include Bangladesh, Solomon Islands, and the United Kingdom – Department of Health of England.[61]
14	**Time and costs to Implement**	Both the time and costs to implement this strategy will be greatly reduced compared to the existing policy in place. Time wise, it will only involve 1 vaccination a year for example at school, as opposed to 2, and costs will be saved across several parts of the program as previously mentioned.
15	**Feasibility and who is involved in generating the data**	Implementing a single dose vaccine program is feasible with modifications to implementation specifically to planning and scheduling, coordination, standardization, procurement, storage and cold chain, safe vaccination, training, social mobilization and communication, vaccination strategies, record-keeping, surveillance, and monitoring and supervision. The Single Dose HPV Consortium (https://www.path.org/programs/center-for-vaccine-innovation-and-access/single-dose-hpv-vaccine-evaluation-consortium/) consists of global researchers actively conducting clinical trials, modeling, and systematic reviews. It is funded by the Bill & Melinda Gates Foundation, coordinated by PATH, and includes Harvard University, London School of Hygiene & Tropical Medicine, Université Laval, University of British Columbia, US Centers for Disease Control and Prevention, US National Cancer Institute, and Wits Reproductive Health and HIV Institute. In addition to the consortium members, representatives from the following institutions serve as advisors: The World Health Organization, International Agency for Research on Cancer; Medical Research Council Unit the Gambia at the London School of Hygiene & Tropical

		Medicine; Instituto Nacional de Salud Pública de Mexico; Quebec Institut National de Santé Publique; Victorian Cytology Service, Australia; University of Washington, USA; and International Vaccine Institute, South Korea.
16	**Regulatory considerations and PQ, are relevant products eligible for PQ**	Licensed HPV vaccines are eligible for PQ submission. Label changes will be at the discretion of vaccine manufacturers and thus this document addresses only a change in policy for HPV vaccination.
17	**National considerations in target countries**	Single dose HPV policy change is global in scope. In some countries the policy change will require WHO recommendation, Gavi concurrence, consideration by NRAs, and might require a label change.
18	**Delivery and implementation considerations**	Use existing routes for delivery including school-based delivery, most common in Gavi countries, with clinic-based delivery supplementary to reach out-of-school girls. A single dose vaccination program could also allow for simpler delivery strategies and taking advantage of existing country-based vaccination campaign schedules such as measles vaccination campaigns. Even vaccinating younger children (< 9 years old) and infants may be advantageous because the coverage of childhood vaccinations (i.e.. Hepatitis B, polio) is generally high, and co-administration of vaccines can also reduce health-services burden in low- and middle-income countries.[62] This might also reduce stigma and vaccine hesitancy associated with HPV vaccine delivery during adolescence. Reaching younger ages may also protect a larger population especially for girls that experience some form of sexual violence. A Gambian phase III RCT (HANDS) is currently ongoing to assess the immunogenicity of 9vHPV in girls 4 – 8 years of age.
19	**Ongoing monitoring after the policy change**	There is monitoring already conducted and required to better understand program coverage in the Gavi HPV technical assistance grants. Monitoring will continue through the Gavi HPV technical assistance grants for those countries receiving Gavi funds, monitoring is conducted and required to better understand program coverage. Further, effectiveness will need to be monitored through real-world single-dose HPV vaccination data and impact studies in countries having implemented a single-dose schedule. Monitoring the prevalence of infection by HPV type among sexually active young women can provide early indication of vaccine effectiveness but it requires considerable commitment of resources for at least 5-10 years which is not suitable for all countries. All countries should establish or improve reporting to comprehensive cancer registries to measure the impact of HPV vaccine programs and of cervical cancer screening. Surveillance should be in place to monitor HPV vaccine safety and investigation of potentially linked serious adverse events.[63] Bruni et al showed that there is a significantly higher uptake of the first dose than the second dose of the vaccine even with ongoing monitoring in place.[64] Low- and middle-income countries performed on average better than high-income countries for the first dose, and worse for the second dose.[65] Monitoring prevalence of infection, reporting to cancer registries, and surveillance of potentially linked serious adverse events should be in place independent of the dosing schedule or funder. Similar monitoring needs exist across dosing schedules. With single dose administration, especially co-administration with other vaccines or within routine immunization programs, monitoring could become easier.
20	**Process and timeline for policy engagement**	WHO SAGE's HPV working group was formed in 2018 and will likely continue to meet and engage through 2022 and beyond. The convening is at the discretion of WHO. Edition 4 of the Evidence Review dated May 2022 has been compiled by the Consortium and is accompanied by a position statement issued by the Consortium. The latter will be revised, as appropriate in view of the WHO SAGE meeting. Available data from ongoing trials with outcomes in 2021 was submitted by the investigators to the SAGE HPV working group. WHO's position paper is expected in December 2022.

21	**Proposed plan going forward**	Here are some next steps going forward: - The Single Dose Consortium with PATH's support will continue to be responsible for consolidating all trial and real-world evidence as well as modeling outputs for HPV single dose and produced updated versions of the Evidence Review - Final KEN SHE and ESCUDDO efficacy results will be ready and report out end 2024 and 2025, respectively - 24-month data is available now for DoRIS and will be available in 2023/2024 for PRIMAVERA and HANDS - Thailand impact study and HOPE study will have final effectiveness results in 2023 and 2024, respectively - CVT year 14&16 immunogenicity data will be available 2023 - Final long-term efficacy data from India-IARC study will be available in 2027 - Modeling work will integrate new data as they emerge from existing evidence and ongoing studies to support countries' decisions regarding policy changes - Additional data from immune compromised trial participants; SAGE has indicated they see this as important information for their decision making. Currently the HOPE trial is enrolling HIV+ persons in their study - WHO's Cochrane analysis will be updated to also feed into the WHO SAGE HPV working group (this is WHO's parallel effort of analyzing all available data on single dose) - Real-world impact studies of 1-dose vaccine schedules may take place in some countries that choose to move forward with implementing 1-dose schedule. These research study designs could provide the first real-life evidence of the effectiveness and operational advantages of 1-dose HPV vaccination alongside ongoing clinical trials[66] - A position paper from WHO on 1-dose HPV vaccination expected in Dec 2022 - Gavi's concurrence for a 1-dose HPV vaccination following WHO's recommendation
22	**Existing use of the proposed policy**	As of June 2020, 107 of 194 WHO Member States have introduced HPV vaccination with an average performance coverage of 67% for the first dose and 53% for the second dose. Low- and middle-income countries performed better on average for first dose but worse on second dose due to high dropout rates.[67] Often girls do not get the 2nd dose after starting the series. While 1-dose has not been implemented yet outside of trials / studies, the expectation is that more girls will be able to get it with the increased focus on getting just one dose. The UK is considering single dose. No country has currently implemented a single-dose HPV vaccination strategy outside of the studies (up to 25,000 girls being vaccinated with single dose through prospectively designed trials/studies).
23	**Minimum Policy Important Difference (MPID)**	The Benefit-to-Cost Ratio (*BCR*) and Savings-to-Investment Ratio (*SIR*) are numerical ratios whose size indicates the economic performance of an investment. The *BCR* is computed as benefits, net of future non-investment costs, divided by investment costs. The *SIR* is savings divided by investment costs. The *SIR* is the *BCR* method recast to fit the situation where an investment's primary advantage is lower costs. In economics, *SIR* is to *BCR* what Net Savings (*NS*) is to Net Benefits (*NB*). Under the conditions established in Burger et al. (2018) with vaccine administration in 9-year-old girls, the crude *BCR* (not adjusted for the discounted time structure of cashflows) for a 2-dose regimen at the 40-year time horizon would be: $BCR = \frac{difference\ in\ proportions\ of\ cervical\ cancer\ case\ costs\ averted,2-dose\ vs.1-dose}{difference\ in\ proportions\ of vaccination\ cash\ outflows,2-dose\ vs.1-dose} = \frac{(21\%-16\%)}{(100\%-65\%)} = \frac{5\%}{35\%} = 0.143$ The 2-dose option for the policy would be considered economically viable relative to the 1-dose base case if the *BCR* were greater than 1.0 (*BCR* > 1.0). But instead BCR << 1.0, so we anticipate that decision-makers should prefer the 1-dose option provided that the conditions in PATH and Burger et al. prevail. The MPID is any combination of numerator and denominator values that gives BCR > 1.0 for the candidate policy compared to the base case. Instead of a crude ratio, however, to properly determine an appropriate MPID level one should prepare a table of cashflows in each time period in the time horizon applicable to the investment decision and calculate the risk-adjusted net present value (*NPV*) of the cashflow differences in the numerator and denominator. The table of cashflows should include projections of locally relevant epidemiological trends in incidence of the target condition and trends in inflation for vaccine acquisition, cancer treatment, labor to deploy vaccination and cancer

		treatment, and other costs. The MPID will depend on the hurdle rate (discount rate) that the decision-makers require for commissioning a new investment, and it is important to determine that each candidate policy that is considered would in fact be approvable based on its favorable *NPV* per the threshold hurdle rate were that candidate policy selected. If annual incidence data are available and the time period over which the cashflows are expected to occur is less than 30 years, then the *NPV* calculations be performed with year periods. For policies that have longer time horizons for cashflows and incident disease-related expenditures, *NPV* calculations on a decade basis may be more appropriate. As before, the MPID is any combination of numerator and denominator values that gives BCR > 1.0 for the candidate policy compared to the base case.

HPV vaccine TPoP references

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