

**Off-label HPV vaccine recommendations:
a survey of NITAGs and EPI program managers**



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Authors and acknowledgements

The survey was developed and reviewed by Paul Bloem, Tracey Goodman, Shalini Desai and Joachim Hombach. Interviews for data collection were carried out by Shalini Desai, Laura Nic Lochlainn, Louise Henaff and Paul Bloem. Analysis and report writing was done by Paul Bloem and final review was done by Laura Nic Lochlainn, Tracey Goodman and Shalini Desai.

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1. Introduction and context

Since 2017, the WHO has recommended¹ a two-dose HPV vaccine schedule for individuals 9-14 years of age, irrespective of the vaccine used (e.g. bi-, quadri- or nonavalent). A six-month interval between doses is recommended for individuals receiving the first dose before 15 years of age. Those aged 15 years or older at the time of the second dose are also adequately covered by two HPV doses.

There is no maximum interval between HPV doses. However, an interval no greater than 12–15 months is suggested to complete the schedule promptly, and before becoming sexually active. If the interval between doses is shorter than five months, a third dose should be given at least six months after the first dose. WHO also recommends a three-dose schedule for those who are 15 years or older, or immunocompromised.

Currently, the supply of HPV vaccine is constrained. This situation is forecasted to continue in the short to midterm.² As a result, countries wishing to introduce HPV vaccine may be delayed in doing so or they may not be able to find the doses required to vaccinate multiple age cohorts in the introduction year.

To optimize the use of the available vaccine supply, in Oct 2019, SAGE will be reviewing the latest evidence on the schedule and maximum interval for HPV vaccine administration. Depending on the evidence and advice from SAGE, WHO could potentially make the following recommendations:

- A. **A three-year interval between the first and second dose of HPV for girls 9-14 years of age** (*Extended interval*) with the justification that this would not only impact the supply situation, but also potentially forgo the need to administer the second dose if the evidence on a one-dose schedule that is expected to become available between 2021-2023 supports the hypothesis that one dose provides full protection.
- B. **Two doses for girls 15-18 years old** (*from currently three doses*)

These WHO recommendations would be de-facto “off-label” recommendations compared to the information provided on the manufacturer’s product inserts (**see Box1 below**).

SAGE requested a survey be conducted to understand the challenges and issues that such potential off-label recommendations would create for NITAGs and EPI managers.³

¹ [Human Papilloma Virus: WHO Position paper, May 2017](https://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf;jsessionid=A54491954A481BBED1349B1C8F2A3FF5). No 19, 2017, 92 WER. 1 (<https://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf;jsessionid=A54491954A481BBED1349B1C8F2A3FF5>)

² [MI4A Global Market Study on HPV vaccines](https://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf;jsessionid=A54491954A481BBED1349B1C8F2A3FF5), Oct 2018 (<https://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf;jsessionid=A54491954A481BBED1349B1C8F2A3FF5>)

³ Neels et al. Off-label use of vaccines. Vaccine 2017. Apr 25;35(18):2329-2337. doi: 10.1016/j.vaccine.2017.02.056

Box 1. Administration, manufacturers' stipulated schedules from produce labels

Bivalent HPV vaccine: For girls and boys aged 9–14 years, a 2-dose schedule (0.5 mL at 0 and 5–13 months) is recommended. The second dose can be given between 5 and 7 months after the first dose. If the age at the time of the first dose is ≥ 15 years, 3 doses (0.5 mL at 0, 1, 6 months) are recommended. The second dose can be given between 1 and 2.5 months after first dose and the third dose between 5 and 12 months after the first dose. If, at any age, the second vaccine dose is administered before the fifth month after the first dose, the third dose should always be administered. The need for a booster dose has not been established. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose. The need for a booster dose has not been established

Quadrivalent HPV vaccine: For girls and boys aged 9–13 years, this vaccine can be administered according to a 2-dose schedule (0.5 mL at 0 and 6 months). If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should be administered. Alternatively, the vaccine can be administered according to a 3-dose (0.5 mL at 0, 2, 6 months) schedule. The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose. However, in clinical studies, efficacy has been demonstrated in individuals who have received all 3 doses within a 1-year period.

Nonavalent HPV vaccine. Girls and Boys 9 to and including 14 years of age at time of first injection Gardasil 9 can be administered according to a 2-dose schedule (see section 5.1). The second dose should be administered between 5 and 13 months after the first dose. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered. Gardasil 9 can be administered according to a 3-dose (0, 2, 6 months) schedule. The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period. Women and Men 15 years of age and older at time of first injection Gardasil 9 should be administered according to a 3-dose (0, 2, 6 months) schedule. The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period. The use of Gardasil 9 should be in accordance with official recommendations.

Source: WHO Prequalified vaccines (https://extranet.who.int/gavi/PQ_Web/Default.aspx?nav=2)

2. Survey methodology

A short questionnaire was developed to assess the potential challenges an off-label recommendation on HPV would pose to NITAGs and EPI managers, and the likelihood the recommendation would be adopted at the country level in the current program context.

The survey was carried out between March and May 2019. The survey respondents were NITAG and RITAG members, as well as EPI managers and other staff within the EPI program. All interviews were conducted in-person or by phone. Respondents were informed the survey was confidential and that countries would be referred to by World Bank income level.

Caveat: several respondents, particularly NITAG members, noted that the responses to the questions represented their personal view only and they could not know what the opinion of other members would be and therefore what the NITAG of their country would decide.

In order to access the target audience, upcoming meetings with NITAG members and EPI managers were identified. Different IVB staff participated as an interviewer, all applying the same questions from the standard questionnaire (Annex 1).

Interviews were carried out during the following meetings (interviewer):

- 1) SEARO NITAG training event (New Delhi March 11-14, 2019) (S.D)
- 2) EPI managers meeting AFRO SEA (Asmara, Eritrea; 18-21 March 2019) (L. N)
- 3) RITAG members attending the Post 2020 meeting (Geneva, end March 2019) (P.B)
- 4) SAGE meeting 2-4 April 2019 in Geneva (P.B, S.D)
- 5) EURO NITAG training for MICs focusing on HPV (Montenegro April 10-12, 2019) (L.H)

Based on feedback by the HPV Working group (April 2019) it was decided to identify a sample size for the survey. As a first step, the total number of “functional NITAGs” (F-NITAGs) was identified through the IVB database (e.g. countries meeting the six criteria reported to WHO through the JRF in 2019). As of December 2018, the total number of F-NITAGs were 99. A further 27 NITAGs exist that do not yet meet all the criteria, several of which had already been included in the sample. A desired sample size of at least 20% of functional NITAGs (overall and per region) was set. Table 1 below shows the final sample.

Table 1: Sample of NITAGs (based on F-NITAGs that meet six WHO criteria. (Source: JRF 2019, April 2019)

		Respondents In Sample			
	F-NITAGs	NITAG	EPI	% of F-NITAG	% F-NITAG incl EPI
AFRO	17	5	3	29%	47%
AMRO	17	4	1	24%	29%
EMRO	13	3		23%	23%
EURO	34	5	3	15%	24%
SEARO	9	7	1	78%	89%
WPRO	9	1		11%	11%
Total	99	25	8	25%	33%
All NITAGs	126 (incl New/not fully functional)				26%

In order to add respondents from under-represented regions, 10 telephone interviews were conducted in April and May (P.B). As a result, in most regions the 20% target was reached, apart from WPRO, which remained slightly under-represented. Overall 25% of functional-NITAGs were included in the sample.

Profile of the respondents and countries

Total number of respondents	35
Total number of countries	33
WHO Regions included in survey	AFR, AMR, EMR, EUR, SEAR, WPR
Countries where HPV vaccination is recommended	21 (65%)
Countries with HPV vaccine introduced (incl sub-nationally)	17 (53%)

Fig 2.1

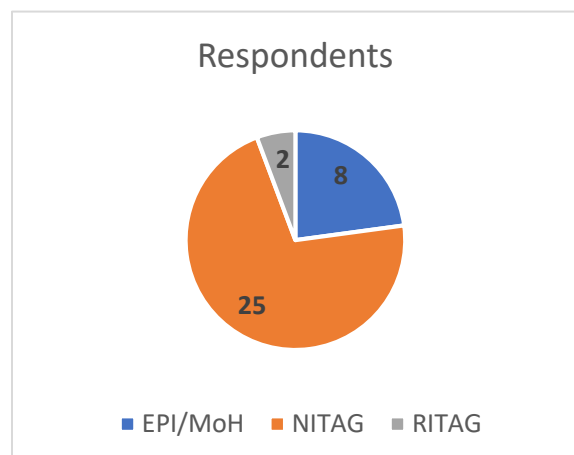


Fig 2.2

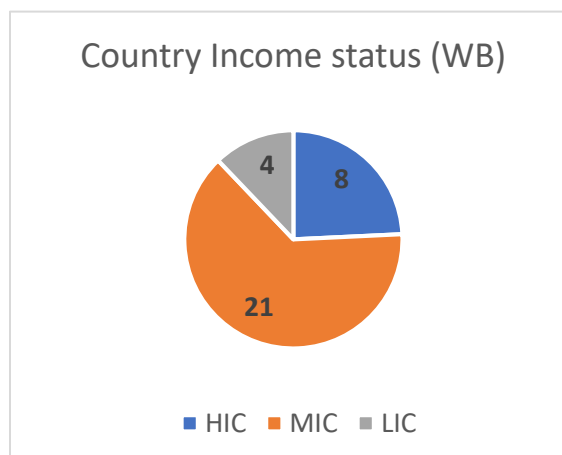
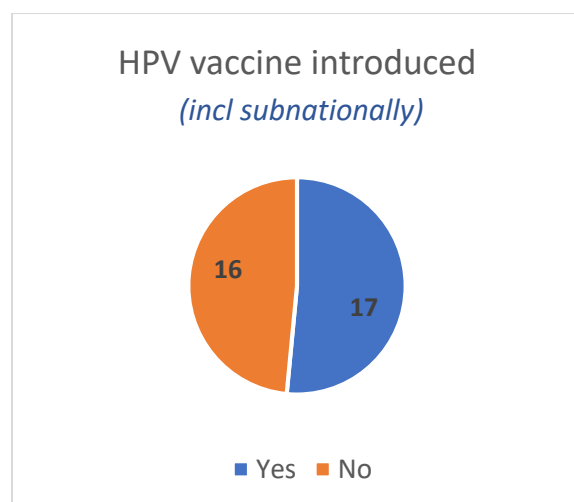


Fig 2.3



3. Results

A. Recommendation for a 1+1 schedule with 3-year interval

Respondents were asked what the main challenges they could see for this recommendation to be adopted. Figures 3.1 and 3.2 show the distribution of the answers (Note: multiple answers possible per respondent).

Fig 3.1 Challenges, all respondents

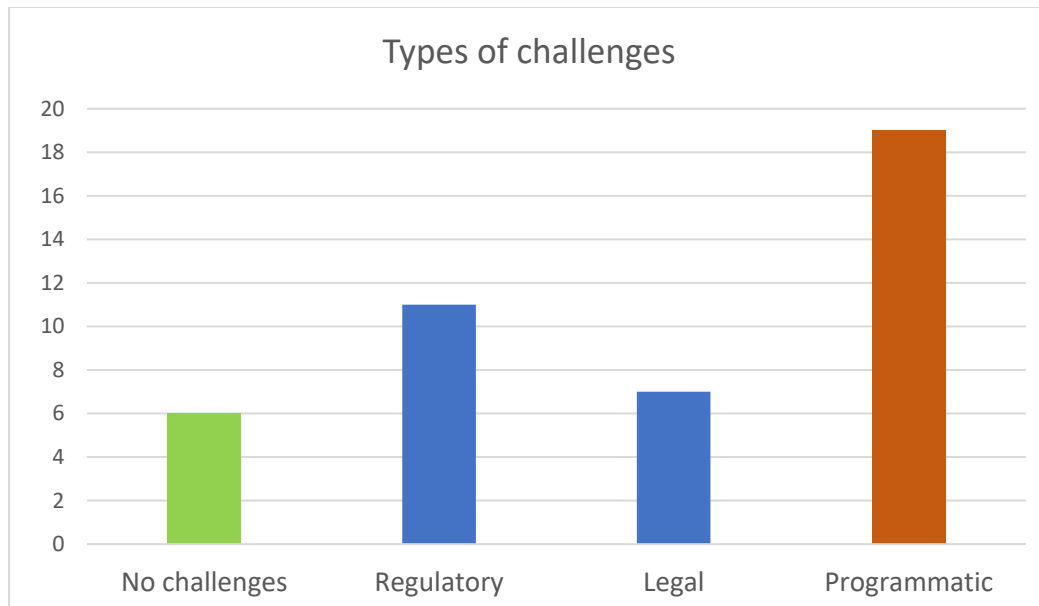
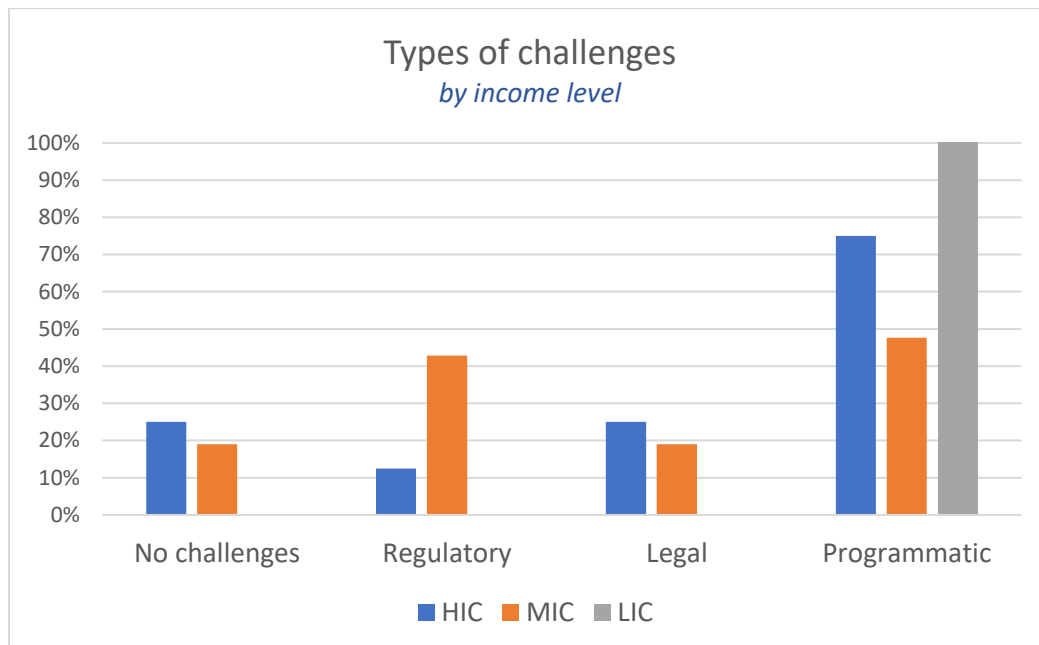


Fig 3.2 Challenges by income level



Programmatic challenges were mentioned most frequently, followed by regulatory issues. Overall, in 70% of countries that have introduced HPV vaccine, programmatic issues were identified. The analysis by income level shows that all LICs (100%) identified programmatic concerns. This can be partly explained by the fact that all the four LICs interviewed have already introduced the vaccine.

Boxes 2-6 represent quoted observations by the respondents on the various challenges and issues raised in this survey that provide insight into the country and program contexts.

Box 2. Observations related to regulatory issues:

“However, it may be a regulatory issue for countries without a strong NITAG and who cannot back-up the MOH decision” (NITAG)

“Would not get implemented due to lack of regulatory buy-in” (NITAG)

“Any off-label recommendation comes with regulatory concern” (NITAG)

“Unclear what the challenges would be in regulation because I joined NITAG just some months ago and NITAG is also young. Could not speak from experience” (NITAG)

“Limited experience in young NITAG with off-label - no experience whether there'd be legal or regulatory challenges. A key issue will be the evidence provided by SAGE.” (NITAG)

“There would need to be evidence/data for the NITAG to make an off-label recommendation” (NITAG)

“They have done off-label recommendations before, the issue would be - is there adequate data to support this change?” (NITAG)

“May have been possible prior to HPV introduction, but now that we have already introduced not possible to change to off-label” (NITAG)

“I am very concerned with the potential inequalities created by lack of supply as well discrimination in the way used in different regions. Ethically it is not acceptable that HPV vaccine not available in African countries. I also have major concerns with the off-label nature of these HPV recommendation as it may put NITAG in uncomfortable situation.” (NITAG)

“Major implications would be with regulator and if the vaccine manufacturer hasn't recognized. Would need to ask special permission from legal every 6 months and would then need to reapply. Nurses would also be frightened to use the vaccine off-label. Any side-effect could have an impact, as the media are very strong.” (NITAG)

Box 3. Observations related to legal issues:

“Off-label itself not worrisome. Depends foremost on strength of the evidence. It would open up countries to eventual legal cases, particularly if HICs continue 2 dose normal schedule; if HICs continue to give 3 doses to girls (and boys) then it is unacceptable.” (RITAG)

“Need to have a dossier from the NRA otherwise it is not possible, ethically can't do and who would take responsibility?” (NITAG)

“Current court case around HPV in progress so respondent could not speculate on what is/is not possible.” (NITAG)

“Country is considering to establish a *vaccination injury compensation mechanism* so we would be looking at potential legal implications of an off-label recommendation.” (NITAG)

“NITAG does not often go off-label. Legal issue is “who has the responsibility?” Normally, the health worker has the responsibility for any adverse effects when a recommendation is as pre the label. When it is off-label it is not clear who has responsibility, the health worker or the NITAG?” (NITAG)

Box 4. Qualitative observations by respondents that see “no challenges” with ‘off-label’

“If evidence is sufficient, off-label not a big issue. RITAG would make this recommendation.” (RITAG)

“Off-label well accepted - no problem to make recommendation. NITAG is discussing some off-label options itself (including on single dose)” (NITAG)

“People listen to doctors, if WHO says it's okay, it could be done” (NITAG)

“We look at evidence. WHO/SAGE more important than insert data. We could consider it” (NITAG)

“SAGE recommendation more important than insert/label, so it could be discussed. However, it would be good to have some evidence on how it would affect coverage” (NITAG)

“This recommendation (on an interval beyond 1 year) has already been suggested in the country NITAG by Ob/Gyns” (NITAG from country that faced a stockout)

“Even though country normally follows the label, in this case off-label not a big challenge if the recommendation comes from WHO. Then it carries a lot of weight.” (NITAG)

Box 5. Observations on programmatic issues

- *In favor of eventual adoption of the recommendation*

“They are working with Ministry of Education to try to improve coverage. However, with the extended interval it would open a window for the second dose, as VHTs could catch up girls by moving house to house to identify girls who only got one dose.” (NITAG)

“This recommendation may re-open the discussion on the interval” (NITAG)

“Currently we vaccinate 10-14 year olds and do multi-age catch up. With the current school based strategy, there might be a few programmatic issues. Not significant in terms of changing of schools, but it can be managed and may be cheaper. We chose to vaccinate annually and cover five cohorts at once. If it was possible to have catch-up in batches (every 3 years), then we would have to visit the schools less often.” (EPI)

“That said, NITAG is always open to review new recommendations from SAGE. It may be used as scenario for sudden supply shortage” (NITAG)

“Country is also looking at an assessment of strategies in case of emergencies, including stock outs. This strategy could be interesting in case of emergency” (NITAG)

“HPV is a very sensitive vaccine - many people are against it and claim it is a ‘vaccine for prostitutes’ Having added flexibility on timing of the vaccination, could be helpful in guiding our decision on timing” (NITAG)

- *Against eventual adoption of the recommendation*

“Currently only giving the vaccine at 10 years and not doing any catch-up. So, there would be a programmatic issue, as they use a 6 month interval now. Teams have been trained in the districts to ensure that girls are captured during that time-period.” (NITAG)

“No problems using off-label. However, this is programmatically not useful, fear to lose girls in schools” (NITAG)

“How would you find the girls for the second dose?” (EPI manager)

“Country uses 6 months interval. Country would not see need to change the current recommendation of 6 months interval to 3 years “ (EPI manager)

“Main reason the NITAG would not implement this recommendation is that 3 years interval is too long, risk of losing girls too high.” (NITAG)

“Would not be adopted because this would create programmatic challenges -particularly tracing the girls” (NITAG)

“Programmatically many constraints. Fear of losing the girls, lack of incentive to move to a 3 year interval given the country doesn’t have a supply challenge.” (NITAG)

“Programmatically the country would not be interested: HPV program is school based in one single grade with a 6 month interval. Moving to 3 year interval would break the system. Our school system is organized in blocs of 3 years, so 3-year interval would mean 2 school types involved” (NITAG)

“Currently we vaccinate at 12 yrs of age. There would need to be a compelling reason to change, it would need to fit into the overall program and there would need to be data for the NITAG to make an off-label recommendation” (NITAG)

Box 6. Observations on “de facto” use of a longer interval

Several countries mentioned that in spite of their reservations regarding introducing a 3-year interval in their HPV program on programmatic grounds, they actually realized that they already “sanction” longer interval, including several years, as witnessed in the quotes below:

“The country uses the 6 months interval. However, anybody who misses the second dose can take it later anytime. The guidance is that anybody can get their second dose even 2-5 years after the first dose, eg. when person already 16-year old. So to some extent we are already recommending the longer interval. That said, we do not see any need to change the current recommendation of 6 month interval” (EPI and NITAG, MIC)

“Actually, the country does already use a longer interval in case a second dose is missed. The guidance is that any first dose is valid and that there is no need to restart the series if more than one or several years have passed.” (NITAG, HIC)

Subsequently, the respondents were asked to consider all the issues previously raised, and to judge whether in their opinion, the NITAG or the country would adopt a 3-year interval recommendation. The following figures show the results by type of respondent (Fig 3.3), income level (Fig 3.4) and by HPV introduction status (Fig 3.5)

Fig 3.3 By type of respondent

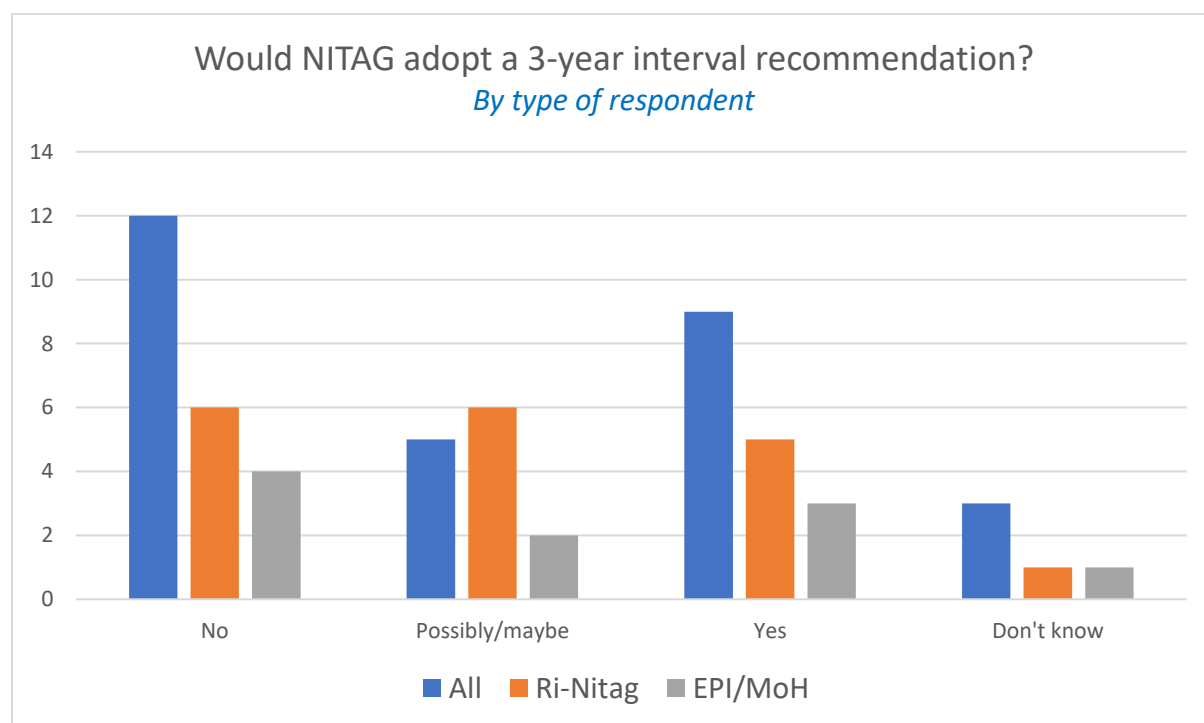


Fig 3.4 By Income level

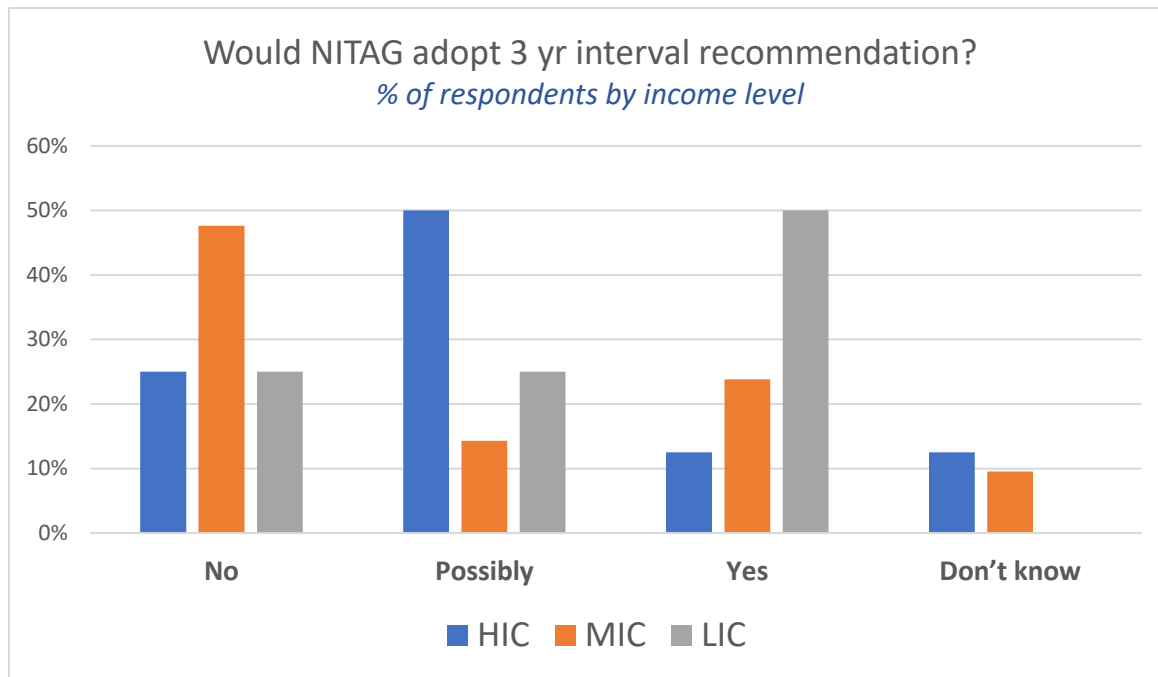
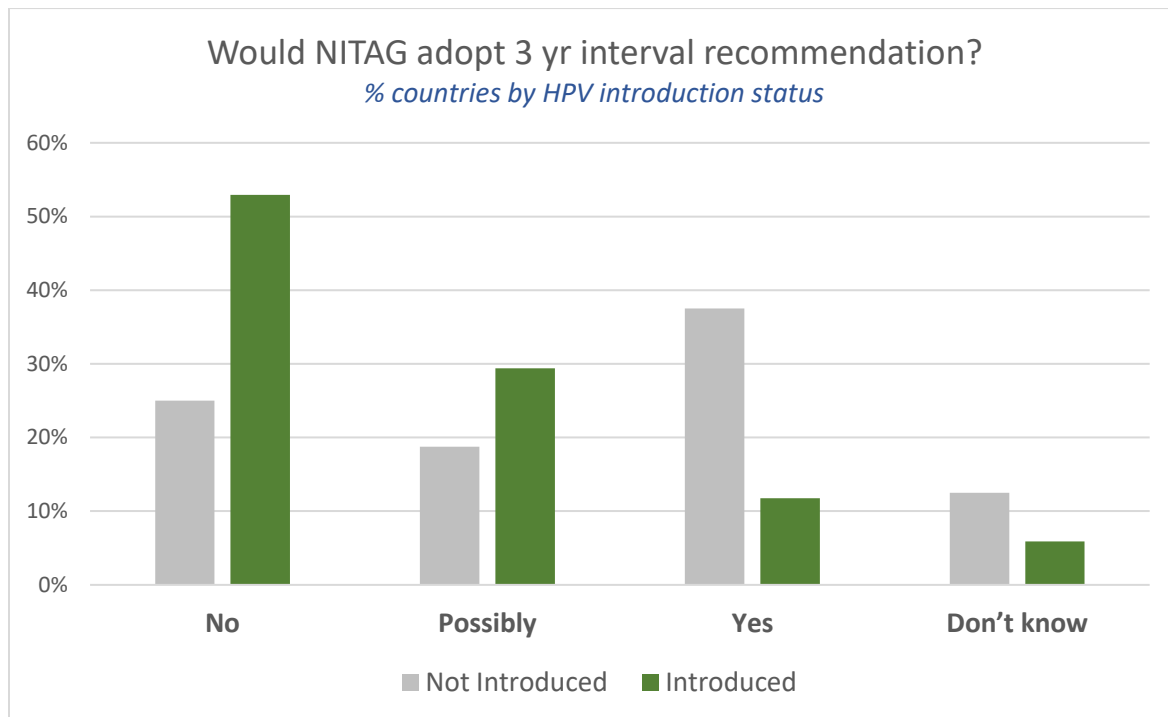


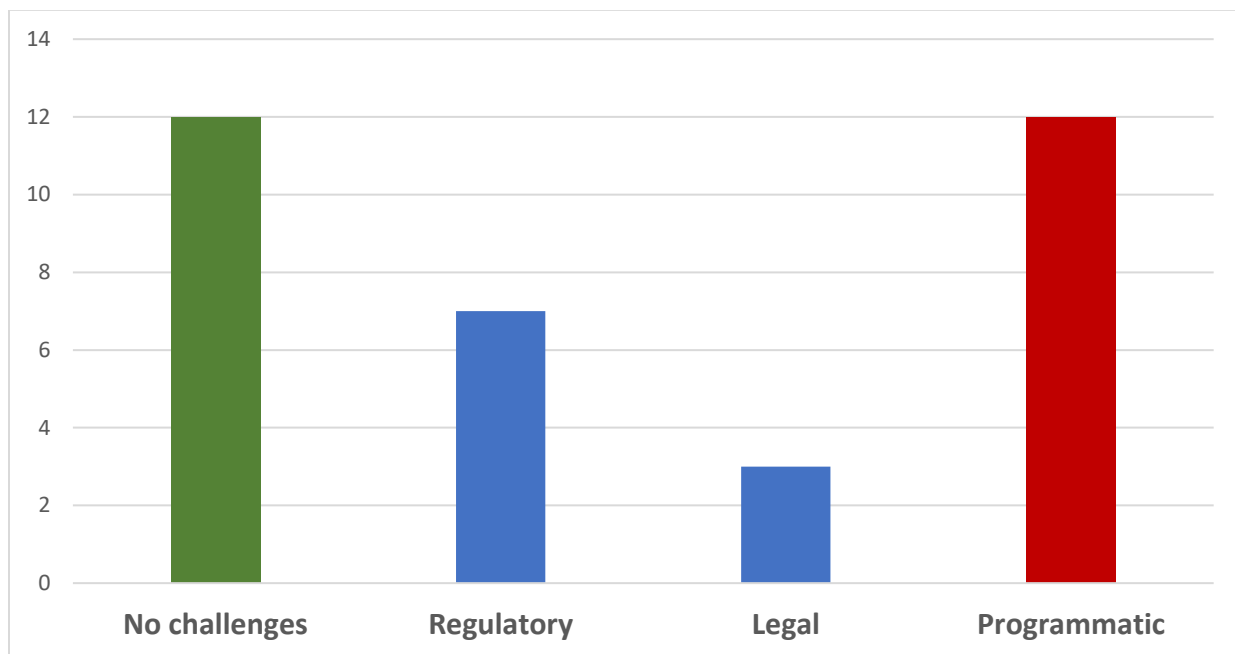
Fig 3.5 by HPV introduction status



B. Recommendation for a 2-dose schedule for 15-18 year olds

The second recommendation respondents were asked to comment on was a potential two-dose recommendation for 15 to 18-year old's (currently 3-dose). Figure 3.6 shows the type of challenges that were mentioned.

Fig 3.6 Challenges for adopting the recommendation of a two-dose HPV schedule for 15-18 year old's



Compared to the responses to the 3-year interval recommendation in the previous section (Fig 3.1), the number of respondents indicating no challenges with this recommendation is considerably higher, while an equally high number cite programmatic issues. This is linked to the likely beneficial impact this recommendation would have for the program – particularly for catch up- and in some cases, to allow for more flexibility on the age of vaccination. For respondents that expressed concerns about programmatic challenges, this age falls outside of the remit and interest of the current program.

The off-label nature of this recommendation was considered to face the same challenges in countries that indicated regulatory and/or legal challenges in the previous question. Beyond the need for strong evidence to justify off-label two-dose recommendation no other specific issues were raised. Overall, there was therefore less in-depth discussion on the off-label nature specific to this recommendation.

In Box 7 selected observations by respondents relevant to these issues are represented.

Box 7. Observations on programmatic issues

Against adopting the recommendation

“This hypothetical recommendation is mostly relevant to new introductions, but given the age of sexual initiation and resources required most countries do not do older age catch up. This age group would be much more relevant if a 1 dose regimen can be used in younger and older ages.” (RITAG)

“What would be much more relevant is being able to introduce earlier (4-8 year)” (RITAG)

“currently the program does not include over 15-year old’s, and it is hard to make HCW and parents do things they have not done before.” (NITAG)

“There is no discussion about (including) older age group” NITAG (MIC)

“Older girls are not really focus of programs in Africa. (RITAG)

In favor of adopting the recommendation

“Same off-label issues, though this is more attractive. All girls have right to catch up till 18 year for any vaccine. 2-dose HPV would be easier and cheaper, so interesting indeed. If the evidence is convincing, we may consider.” (NITAG)

“Currently girls and women up to 26 are eligible so this recommendation would surely be interesting and quite surely be reviewed and most probably adopted.” (NITAG)

“Same off-label issues: OK if evidence strong. The issue of vaccination at older age as a strategy was discussed in NITAG because some states think this could be more acceptable. Therefore, the 2 dose off-label recommendation would be very welcome as an option.” (NITAG)

“If the recommendations come with evidence then the off-label nature no problem. This would be very welcome programmatically - 12 years is considered very young in our culture. Vaccination towards the end of high school, around age 16 or 17 would be a good timing programmatically and for cultural acceptance.” (NITAG)

On the question whether the NITAG would adopt the two-dose recommendation for 15-18-year old’s, slightly more respondents thought this recommendation would not be adopted than those favoring adoption (**Fig 3.7**). When analyzed by income level (**Fig 3.8**) it becomes clear that HICs are most likely to adopt this recommendation, and LICs least likely. This reflects the fact that older age groups are more often past of the catch-up target in HICs, while in LICs GAVI does not provide doses for this age group. Disaggregated by introduction status (**Fig 3.9**), relatively more countries with existing programs (most of which are MICs and LICs that do not cover this age range) would hesitate to change the vaccination target age.

Fig 3.7

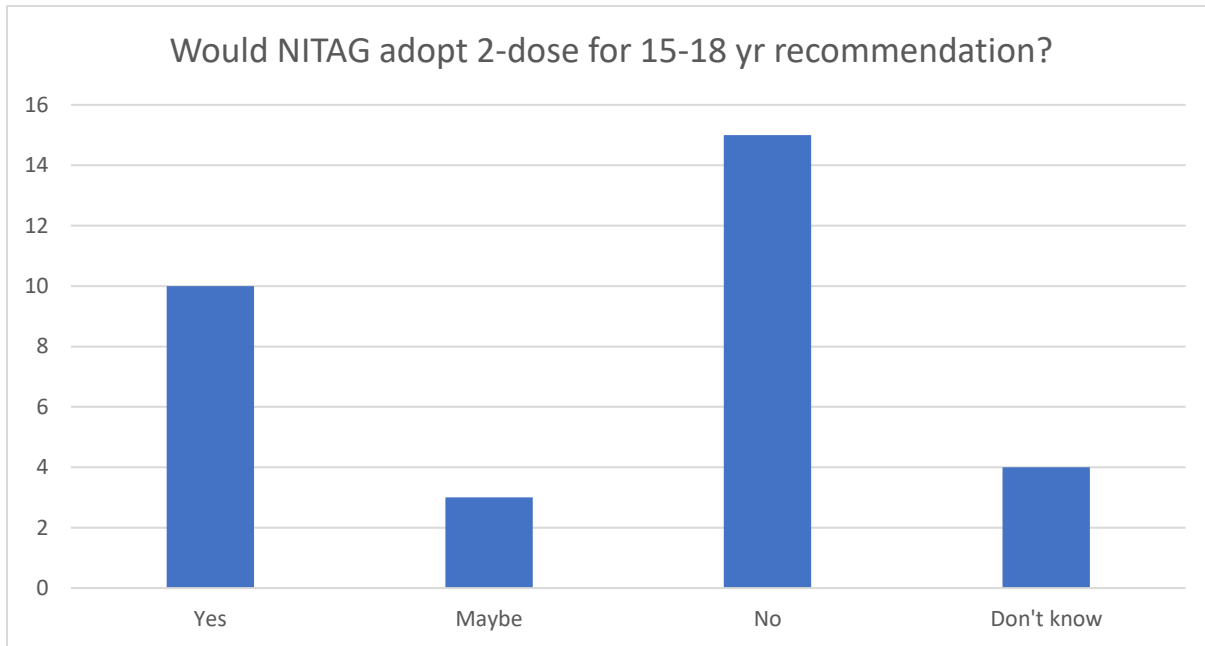


Fig 3.8

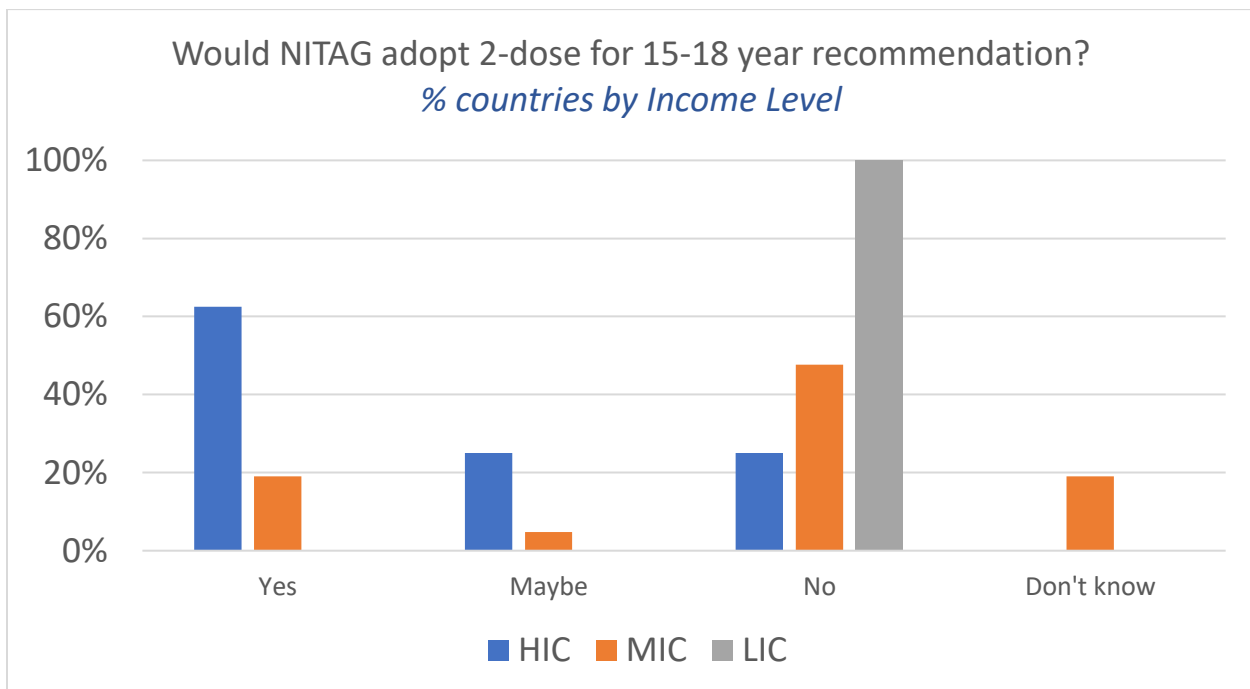
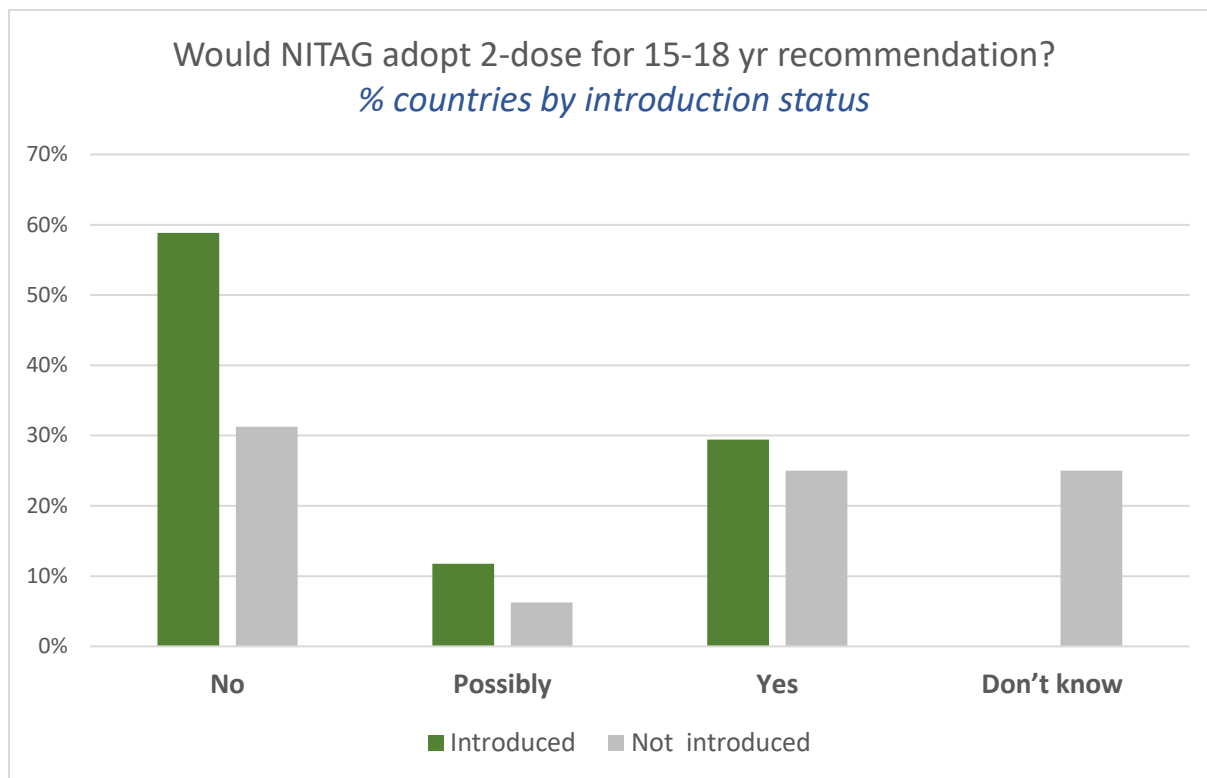


Fig 3.9



4. Conclusions

Off-label use

As has been shown in articles on the off-label use of vaccines^{3,4}, there is widespread use of off-label recommendations in vaccination. The article by *Top et al.*, identified that more than half of countries have used off-label vaccine recommendations.⁴

While for some NITAGs the off-label nature of the potential WHO recommendations on HPV is problematic and potentially a barrier to implementing it, the majority of NITAGs interviewed were open to consider an off-label recommendation. For many, the strength of the evidence behind the recommendation and the fact that SAGE had reviewed the evidence and WHO was making such a recommendation outweighed the off-label nature.

Three-year interval

There was hesitancy among a majority of countries to adoption the potential 3-year interval recommendation, particularly among countries that have already introduced the HPV vaccine based on programmatic reasons. A smaller proportion of countries identified opportunities in the increased flexibility this recommendation would bring. Countries that have not recommended HPV vaccination nor introduced the vaccine were more open to consider this 3-year interval recommendation

Two dose schedule for 15 to 18 year olds

The majority of countries are currently not targeting older adolescents in their HPV programs or introduction plans (including GAVI supported countries). This may explain why there was limited interest in adopting the recommendation. For those countries with catch-up or ongoing vaccination in older populations, this recommendation was very welcome. For a small group of countries, this recommendation would be an opportunity to identify a routine target age beyond the 9-14 years of age that WHO currently recommends.

4 K.Top et al., Governing off-label vaccine use: An environmental scan of the Global National Immunization Technical Advisory Group Network; submitted for publication 2019.

Annex 1: Off-Label interview guide/Questionnaire

Country provide name or WB income status	Country:	HIC	MIC	LIC
Respondent	NITAG	RITAG member	EPI manager	
NITAG has made an HPV vaccine recommendation	1. Yes		2. No	
HPV vaccine introduced in the country	1. Yes		2. No	

Off-label recommendation: Extended interval: second dose after 3 years.

- For your country to adopt this “off-label” recommendation, what are the main challenges you see? *(Probe on the dimensions below, circle any dimension that is mentioned)*
 - ☐ Regulatory (licensing)
 - ☐ Legal
 - ☐ Programmatic (stakeholder perceptions and impact on implementation)
 - ☐ NONE

Please elaborate:

- Do you think your country would adopt the recommendation (despite being off-label)

YES
NO
DON'T KNOW?

Off-label recommendation: Reduced doses: 2 doses for 15-18 year olds.

- For your country to adopt this “off-label” recommendation, what are the main challenges you see? *(Probe on the dimensions below, circle any dimension that is mentioned)*
 - ☐ NONE
 - ☐ Regulatory (licensing)
 - ☐ Legal
 - ☐ Programmatic (stakeholder perceptions and impact on implementation)

Please elaborate:

- Do you think your country would adopt the recommendation (despite being off-label)

YES
NO
DON'T KNOW?