Facilitators and Barriers to Future Group B *Streptococcus* Vaccines. A Global Perspective.

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Content

1. Brief overview of Group B *Streptococcus*
2. GBS vaccines on the horizon
3. Facilitators and barriers to maternal vaccination
4. Maternal perspectives on GBS vaccines (USA, Ireland, Dominican Republic
5. Provider perspectives GBS vaccines (USA, Ireland, Dominican Republic)

GBS infection in infants

Presentation in Infants	Prevention strategies
Sepsis/bacteraemia Pneumonia Meningitis Skin, soft tissue & musculoskeletal infections Neonatal encephalopathy Stillbirth* Preterm delivery* **<u>Three clinical entities in infants</u>** Early-onset infection (0-6 days of life) Late-onset infection (7-89 days) Late-late onset infection (≥90 days)	**<u>Early-onset infection:</u>** 1. Universal microbiologic screening 2. Risk-based approaches -Clinical risk factors -Targeted intrapartum GBS-PCR **<u>Late-onset infection</u>** No effective preventative strategy

*Association not clearly defined

Global Burden of GBS Infection.. Momentum!

>90,000 Infant Deaths each year

>40,000 Stillbirths each year

Significant long-term disability

"This new research shows that Group B strep is a major and underappreciated threat to newborn survival and wellbeing, bringing devastating impacts for so many families globally. ***WHO joins partners in calling for urgent development of a maternal GBS vaccine, which would have profound benefits in countries worldwide."….***

Dr Philip Lanbach, WHO October 2021

Why is a GBS vaccine needed?

- Burden of late-onset infection
- Feasibility of screening in low-resource regions
- Limitations of risk based and microbiologic screening
- Impact on pre-term delivery and stillbirth
- Concerns about antibiotic related harm

GBS vaccines in development

GBS vaccine candidates in preclinical and clinical trials

Vaccine Candidate	Preclinical	Phase I	Phase II	Pregnant women (I/II)	Phase III
Monovalent and bivalent conjugates (CRM197-CPS)	X	X	X	X	
Trivalent conjugate vaccine	X	X	X	X	
Hexavalent Conjugate vaccine (GBS6) (Pfizer)	X	X	X	X	
N-terminal domains of Rib and Alpha C proteins (GBS-NN/N2) (Minervax)	X	X	X	X Results awaited	
Pilus and other proteins	X				

History of GBS vaccines

1970's Carol Baker and colleagues defined the structure of the capsular polysaccharide III and demonstrated proof of concept of a capsular polysaccharide vaccine.[1,2]

The NEW ENGLAND JOURNAL of MEDICINE

"It seems a paradox that at a time when suitable and safe candidate vaccines are nearly ready for clinical trials, these issues provide seemingly insurmountable obstacles to clinical investigators…However, these frustrations are common among those who suggest that maternal immunisation will safely provide improved outcome for both the young infant and the mother. Perhaps the final decade of the century will see the conquest of more than one encapsulated organism afflicting young infants."
Carol Baker JID 1990

1. Baker CJ, et al. Quantitative determination of antibody to capsular polysaccharide in infection with type III strains of group B Streptococcus. J Clin Invest. 1977;59(5):810-8.

2. Baker CJ, Kasper DL. Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infection. N Engl J Med. 1976;294(14):753-6.

GBS vaccine: Why has it taken this long?

- Challenges conducting trials in pregnant women
- Understanding the true global burden of disease
  - Global epidemiology: Geographic variation in serotypes and invasive disease
  - Stillbirth
  - Pre-term delivery
  - Hypoxic Ischemic encephalopathy
- Defining end points for phase 3 trials
- Implementation challenges
  - Vaccine uptake in pregnancy
  - Integration of vaccine in pre-existing GBS prevention strategies

Maternal vaccine uptake: Key influencing factors

Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review

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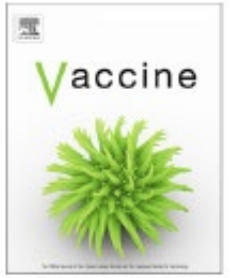
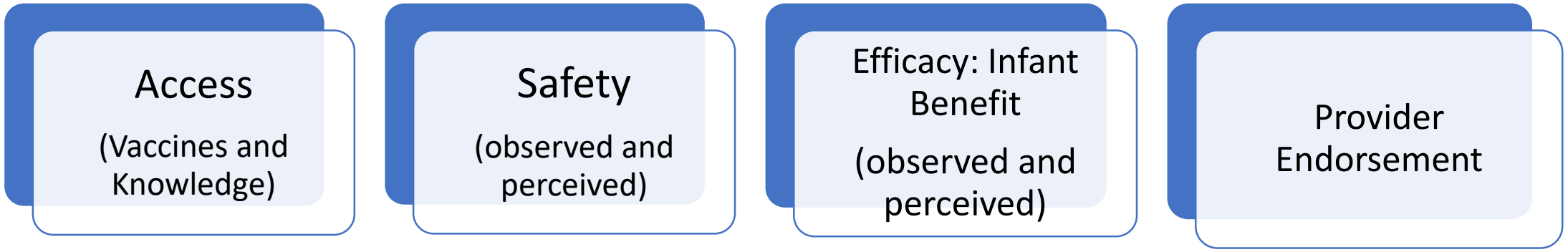


Differential impact of factors can be both vaccine and context specific

Maternal vaccine: uptake key influencing factors



Research design

Maternal Perspectives

Cross-sectional mixed methods survey with pregnant women in the US (Philadelphia) and Ireland (Dublin) N=502

Cross-sectional mixed-methods survey with pregnant women in the Dominican republic (DR) (Three sites) N=650

Provider perspectives

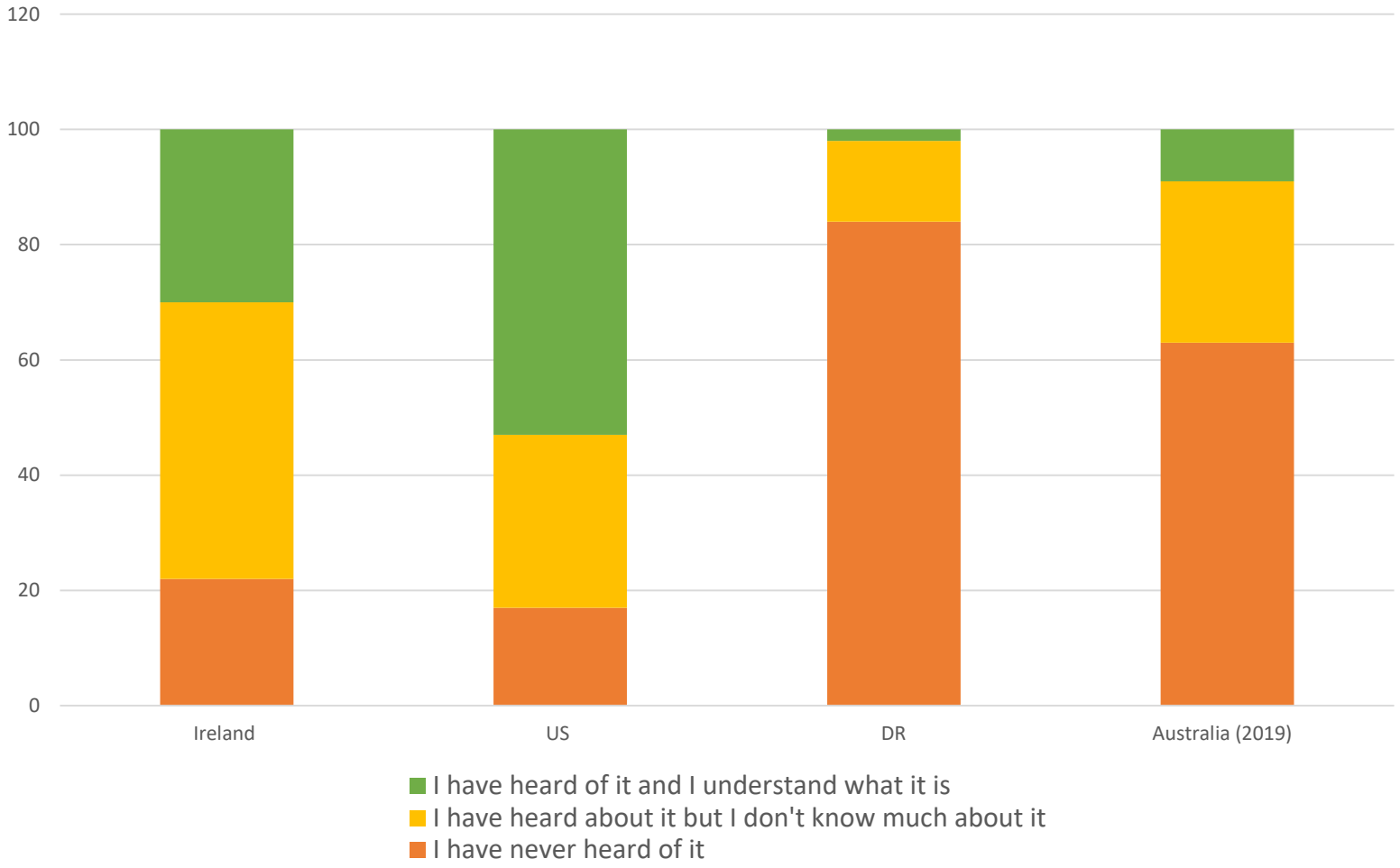
Qualitative survey with maternity care providers in the US, Ireland and the DR N=70

Background: Country Contexts

	United States	Ireland	The Dominican Republic
GBS maternal colonization rate	20-25%	11-19%§	20-25%§
Neonatal infection	EOS:0.2/1000 live births LOS:0.3/1000 live births	EOS: 0.45/1000 live births LOS: 0.29/1000 live births	EOS: 2.35/1000§
National guideline	Universal screening and intrapartum antibiotics.	Risk based approaches Universal screening Targeted PCR testing	Universal screening and intrapartum antibiotics, but not widely implemented.
Maternal immunization programme	TDaP, Flu, COVID-19* Administered in obstetric practices**	TDaP, Flu, COVID-19* Administered in mostly General Practice	TD, Flu, COVID-19* Administered at Immunization centres
Uptake of recommended vaccines in pregnancy	Flu:61%, TDaP:57% (2019-2020)	Flu: 62% TDaP: 50% (2017)	PAB against tetanus: 90% (2014)
Maternity care delivery	Obstetrician/Midwife lead 99% of births in a health facility	Obstetrician/ Midwife led Shared care with general practice 99% of births at health facility	Obstetrician led 97% births in health facility

*Introduced in 2021 **varies throughout the US § Limited data available

Maternal Perspectives: Knowledge of GBS



Maternal Perspectives: acceptability of a GBS vaccine

Following receipt of information regarding a future GBS vaccine and infant benefits acceptability was high among each group:

- Likely receipt of a GBS vaccine measured on a 10-point scale US and Ireland: 9 (IQR 8-10) [1]
- In the DR, 611/650 (94%) responded that they would be likely or very likely to receive a GBS vaccine .
- Consistent with other studies in US [2], UK[3] , Australia[4]
- In a study of 495 pregnant women in Melbourne[4], When asked to compare vaccination with intrapartum antibiotics, the majority of women (440, 89%) stated they would prefer to receive a GBS vaccine.

1.Geoghegan et al. Preparing for Group B Streptococcus vaccine. Attitudes of pregnant women in two countries. Hum Vaccin Immunother. 2023 Dec 31;19(1):2195331
2.Dempsey AF et al. Acceptability of a hypothetical group B strep vaccine among pregnant and recently delivered women. Vaccine. 2014;32(21):2463–8.
3. McQuaid F et al. Attitudes towards vaccination against Group B Streptococcus in pregnancy. Arch Dis Child. 2014;99(7):700–U104. doi: 10.1136/archdischild-2013-305716.
4. Giles ML et al. Pregnant women's knowledge and attitude to maternal vaccination including Group B Streptococcus and respiratory syncytial virus vaccines. Vaccine. 2019;37(44):6743–9.

Infant benefit as a strong motivator for maternal vaccination

Responses to open-ended question *"Why would you be likely or unlikely to receive this vaccine?"*

"If it would protect my baby of course I would get it" (IRL)

"I'd do it to protect my baby" (US)

"I would do anything to protect my baby" (US)

Barriers to GBS vaccination: Concerns about novel vaccines

Responses to open-ended question *"Why would you be likely or unlikely to receive this vaccine?"*

"Probably skeptical as it would be so new" (Irl)

"I don't think I want to do any new vaccine" (US)

"Because it is a new vaccine I will not trust it. If after a time I see that it works well in the others, I would get it." (DR)

"I'd want to know more information on long term effects on the baby" (US)

"I would need additional research results on the long-term effects of the vaccine for myself & my unborn child" (US)

Perceptions around current GBS strategies

"

"I feel if GBS was that big of a risk we would routinely test for it, which doesn't happen in Ireland. Therefore, the leap from not testing to vaccine seems quite a leap" (IRL)

"May not make the 4 hours for antibiotics" (US)

"I would get the vaccine if it was essential for the babies health, but I would prefer to take antibiotics" (IRL)

"Surely widespread vaccination has to be preferable to widespread use of antibiotics? That would be my main feeling on this" (IRL)

Provider recommendation is particularly important for novel vaccines

"I would be very cautious with a new vaccine, but I would be likely to take it if recommended by a consultant." IRL

"I would want to learn how likely it was I was to have it, seems like if you could just get tested and treated maybe the need for a vaccine is less? However, not strongly opposed and would follow doctors' direction" US

"I would be likely to get this if it was advised by my midwife/doctor for the benefit of me and my baby" IRL

Acceptability of a GBS vaccine: Provider perspective

Maternity care provider acceptance of a future Group B *Streptococcus* vaccine – A qualitative study in three countries

Sarah Geoghegan [a,b,c,*], Francia Acosta [d,e], Laura C. Stephens [c], Hanah Gillan [c], Sandra Valera [f], Richard J. Drew [g,h,i], Maeve Eogan [j], Adam J. Ratner [k], Andrew P. Steenhoff [b,d], Karina M. Butler Kristen A. Feemster [b,d,l]

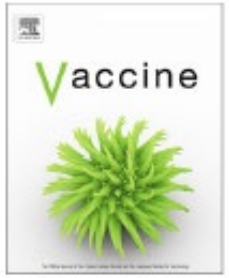


Table 2
Characteristics of interview participants.

	US N = 16	Ireland N = 34	DR N = 20
Provider type	Obstetricians (9) Midwives (5) Family Medicine (2)	Obstetricians (9) Community Midwives (9) General Practitioners (16)	Obstetricians (20)
Gender(M/F)			
Obstetricians	1 M 8F	5 M 4F	4 M 16F
Midwives	0 M 5F	0 M 9F	N/A
General Practice	1 M 1F	6 M 10F	N/A
Healthcare setting	Five different obstetric practices & one family medicine practice all within the Penn medicine group.	Three tertiary and one regional Hospital. Fourteen different General Practices.	Tertiary, regional, and municipal hospital.
Geographic location	Philadelphia (16)	Dublin (23) Outside of Dublin (11)	Santo Domingo (11) San Pedro (7) Consuelo (2)

M: Male F:Female.

Results: Principal concepts

1. Beliefs about benefits and downsides of local early-onset GBS prevention strategy influenced perceptions about a new vaccine, this varied between providers and countries.

2. Dept of knowledge and experience of GBS varied by provider type and country and influenced opinions on a GBS vaccines.

3. Ease of integration into existing strategies was important to providers.

4. Attitudes towards vaccines in pregnancy, more generally impacted views on GBS vaccines.

Perceived advantages of a GBS vaccine

Reduce perinatal interventions

‘‘I think it (a vaccine) would allow us to relax our recommendation for induction of labour for women that we have. And for sure, that is something that would, for lots of women, be their wishes. . .if we’re looking at women centered care. . . then we can have a completely different discussion with them about their options at that point, and perhaps, like push our guidance out” Obstetrician, Ireland.

A vaccine is a more feasible alternative in poor resource settings

‘‘Always, when we talk to patients about something that could benefit their patients and their baby, they are open to it, but what comes to mind is if we have resources available and the availability of the laboratory to do the test. You know that sometimes the system lags with some things and as doctors our hands and feet our tied even if we intend to do things.” Obstetrician, DR

Reduce antibiotic use

‘‘I do think there is some patients and also physicians have an increasing concern about the microbiome and how we’re affecting that with antibiotics. So, the idea of a way to prevent GBS disease without use of antibiotics, I think is attractive.” Obstetrician, US

Impact on Late-onset infection

‘‘No, I don’t really think it comes up in our practice very much,.., I don’t think we think much about late-onset because that’s firmly in the realm of paediatrics.” Obstetrician, US

Concerns about a GBS vaccine

"Is it worth vaccinating every-one for 25 %?"

"I guess my thought is. . . what is it, maybe only 25 % of the women are colonized with Group B *Strep*, so is it worth vaccinating every-one for 25 %? I don't know. And in nonpregnant women it's not even considered a pathogen" M**idwife, US**

". . .So, yes I think we'd have to have pretty good, kind of, evidence before we would embark on vaccinating everybody, you know? And then, yes, I suppose, then, you know, you've got like 30–35 % of women who will be delivered by caesarean section, and, you know, then- so, you know, is that going to be 30 % of women who are getting a vaccine unnecessarily?" **Obstetrician, Ireland**

Too many vaccines

"I do wonder…Like, I am very pro-vaccines, but I do think, Oh God, even about the amount of vaccines babies get. I know they need them all and if I had kids they would be vaccinated,…. but you do wonder where do we stop in the line of progress?" **Community midwife, Ireland**

"so that will be a 4th vaccine added for pregnant women, I myself would be concerned if I was a pregnant woman getting so many vaccines and how that would impact on the baby later in life. That is the main concern pregnant women have anyway. Because, if we roll out the vaccine it will be universal, we would be giving the vaccine to everyone" **Obstetrician, Ireland**

Provider recommendation. Advocates Vs Information givers

"So I won't say, you know, I recommend. But I will say the HSE recommends them as well. So because I think you can sway people quite easily as a healthcare professional. And I'm kind of reluctant to sway them into, you know, to what I think..." **Community Midwife, Ireland**

"I guess those vaccines that have been tried and trusted ..I'd be very strongly advocating. It's often a question we've had amongst ourselves in this hospital as to whether or not we should be strong advocates or do we just give the information and the let decide. My feeling has always been more the fore, but I know there are colleagues of mine who feel that we're not in that position to do so and we are there as information givers." **Obstetrician Ireland**

"It's a tricky one. I am very reluctant to say this is what I'd do, because that's my whole, everything that's going on with me influences that. So, I would generally say, the important thing here is that you make the decision that feels right for you. **GP, Ireland**

"They are happy for you to- if they're a bit hesitant, they're happy for you to take the reins and tell them you should have it." Then they're like, okay sort of thing**. GP, Ireland**

"And sometimes they ask me what's my personal take on it. And I say, I have a get out clause which one of the other midwives gave me, which is, you know, all I can tell you is these are the HSE recommended vaccinations. Which is my, it is my way of getting out of making a personal recommendation. Because I would feel weird about doing that, you know. I kind of want to leave myself out of it." **Community Midwife, Ireland**

What influences approaches to vaccine communication by maternity care providers?

- Ethos: Autonomy, shared decision making, a view that personally endorsing a vaccine can compromise the principle of autonomy.
- Confidence in safety of vaccines in pregnancy (in turn influenced by available data. This may be vaccine specific).
- Experience as vaccinators (GPs vs obstetricians vs midwives).
- Knowledge, dissemination of information.

Provider confidence in maternal vaccines can be fragile.

"The spectre of Thalidomide"

"... And there's always the spectre of thalidomide hanging in the back to us" **Obstetrician, Ireland**

"I agree with vaccines as I told you because they save lives. But still, one must research well and take a little more time in pregnant women because we are not talking of a regular person we are talking of a pairing where there is another living being, we don't know what could happen and we should not play with organogenesis." **Obstetrician, DR**

Too many vaccines

"Like, I am very pro-vaccines, but I do think, Oh God, even about the number of vaccines babies get….where do we stop in the line of progress?" **Community midwife, Ireland.**

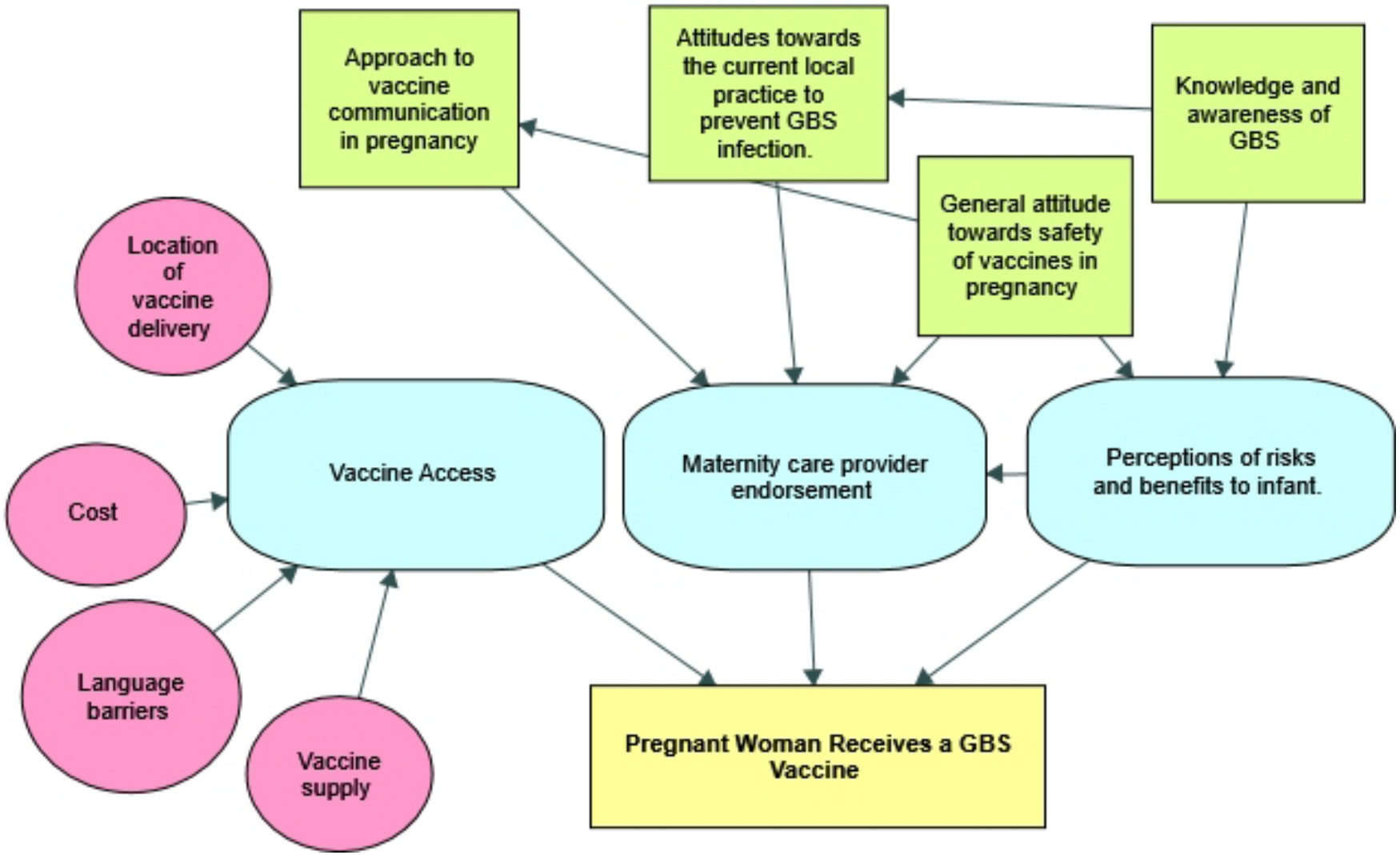
Approach to the first trimester "

If someone came to me and asked me for the advice I would say, yes, probably just hold off until after the first trimester, and I don't-That's just sort of a reflex answer rather than something that I know that there's any evidence for." **Obstetrician, Ireland**

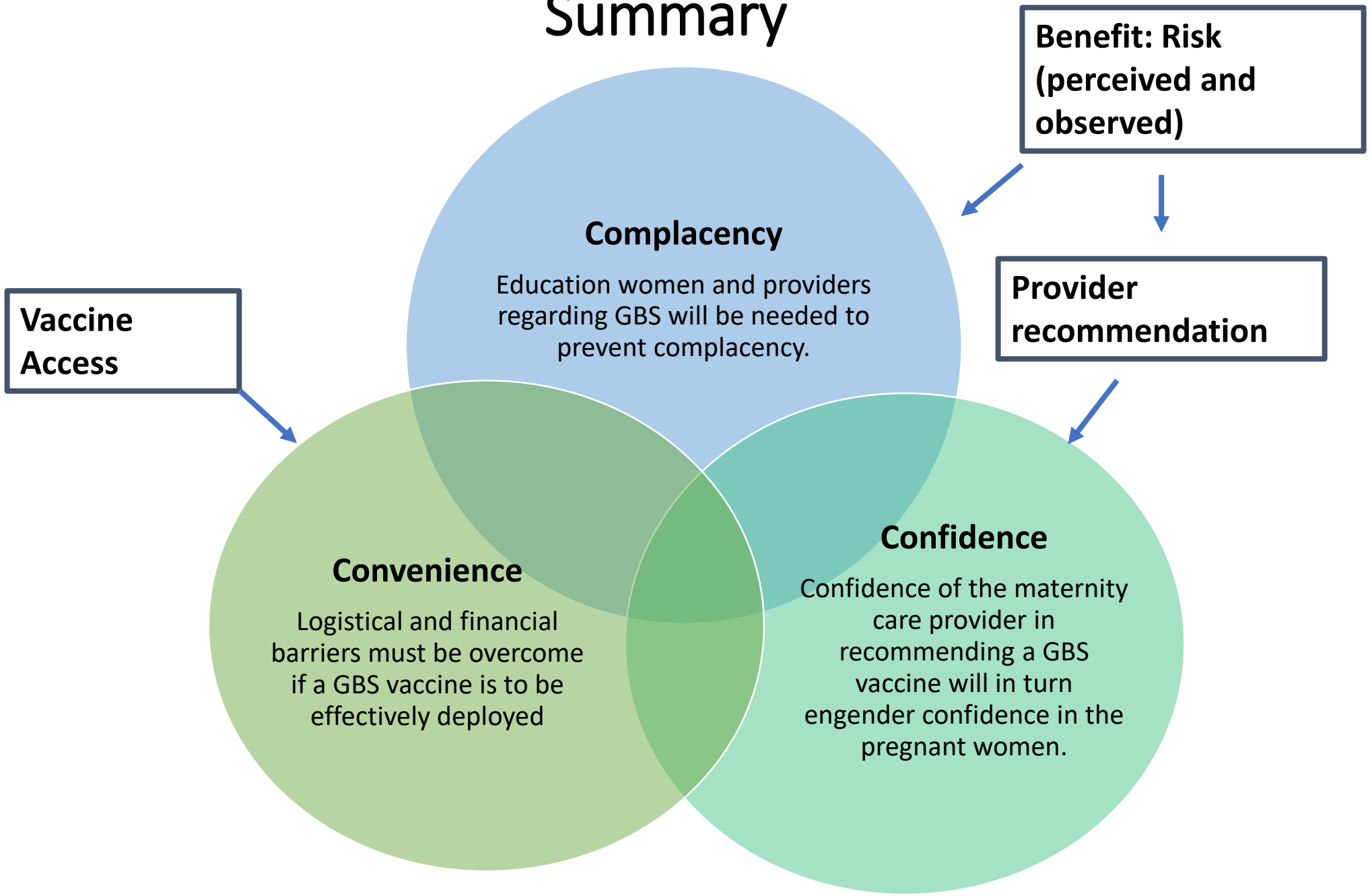
"Is it worth vaccinating everyone for 25%"

"I think although we think vaccinations are safe, in pregnancy, in particular, we're always aiming to do the minimum amount that is safety required and so it seems counter-intuitive to that idea, to be vaccinating women against something that 60-some per cent of them may not ever require, ever." **Midwife, US**

Acceptability of GBS vaccine



Summary


Benefit: Risk (perceived and observed)
Provider recommendation
Vaccine Access
Complacency
Education women and providers regarding GBS will be needed to prevent complacency.
Convenience
Logistical and financial barriers must be overcome if a GBS vaccine is to be effectively deployed
Confidence
Confidence of the maternity care provider in recommending a GBS vaccine will in turn engender confidence in the pregnant women.

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