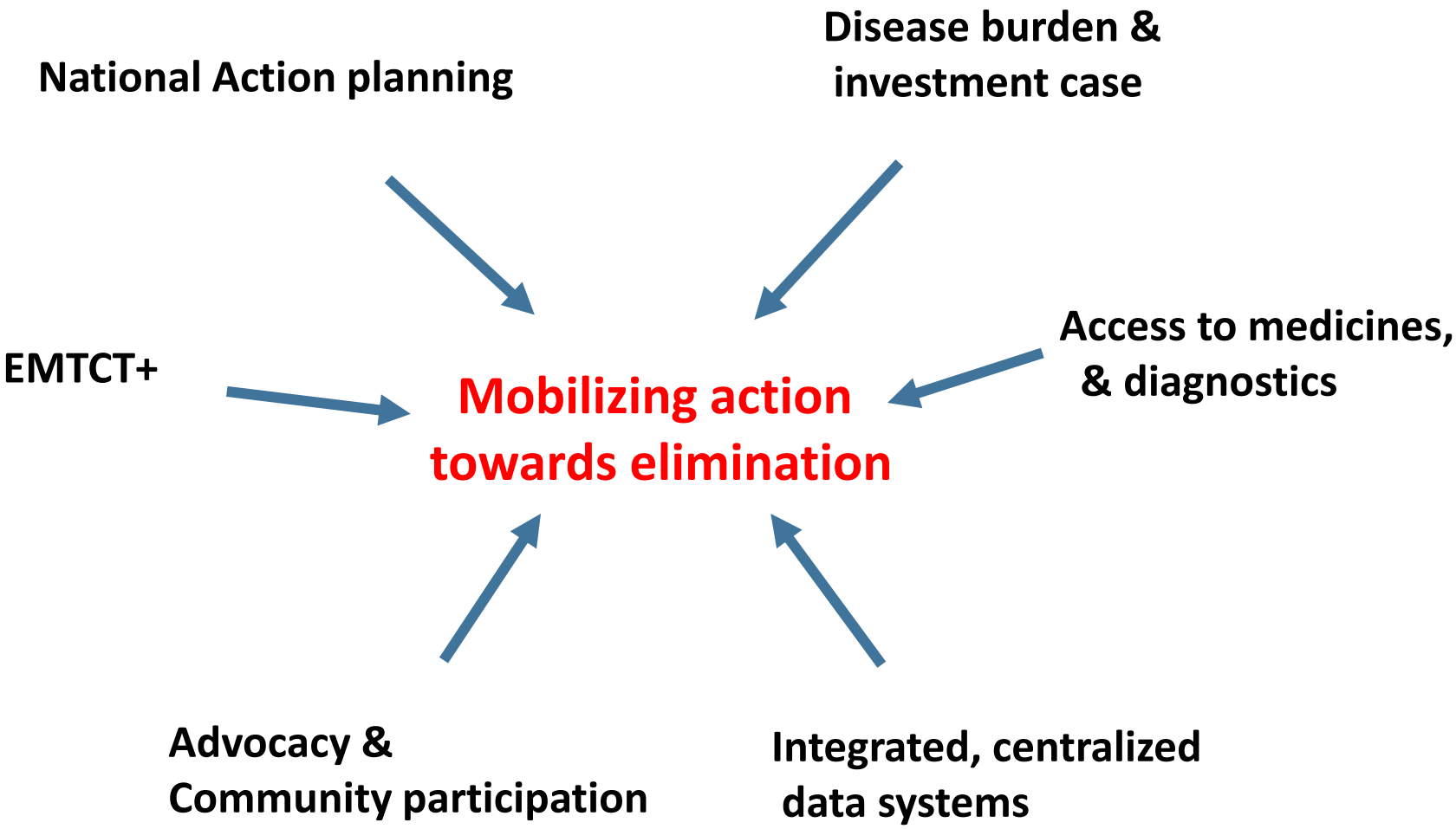
PAHO's Comprehensive support to address hepatitis



Hepatitis treatment – status in 2018

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Organización Mundial de la Salud

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Hepatitis treatment is liver cancer (HCC) prevention

Ideal scenario

Curative treatment

+

Highly effective vaccine

Ideal scenario

Curative treatment

+

Highly effective vaccine

Both cheap and safe

Hepatitis C

cDAAs cure
> 95%

+

No vaccine

Hepatitis C

cDAAs cure
> 95%

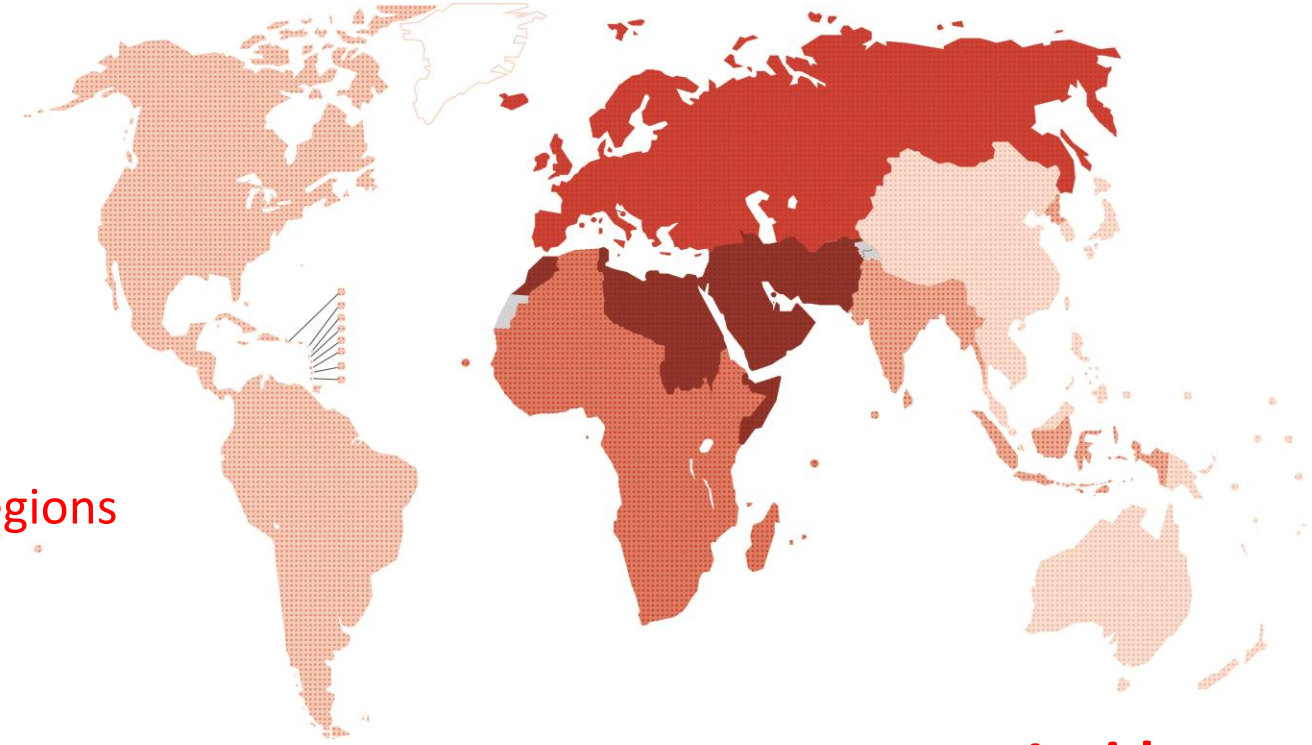
IPC +
Safe infections +
Blood screening +
safe sex +
harm reduction

Varies in expense and safety

HEPATITIS C TREATMENT

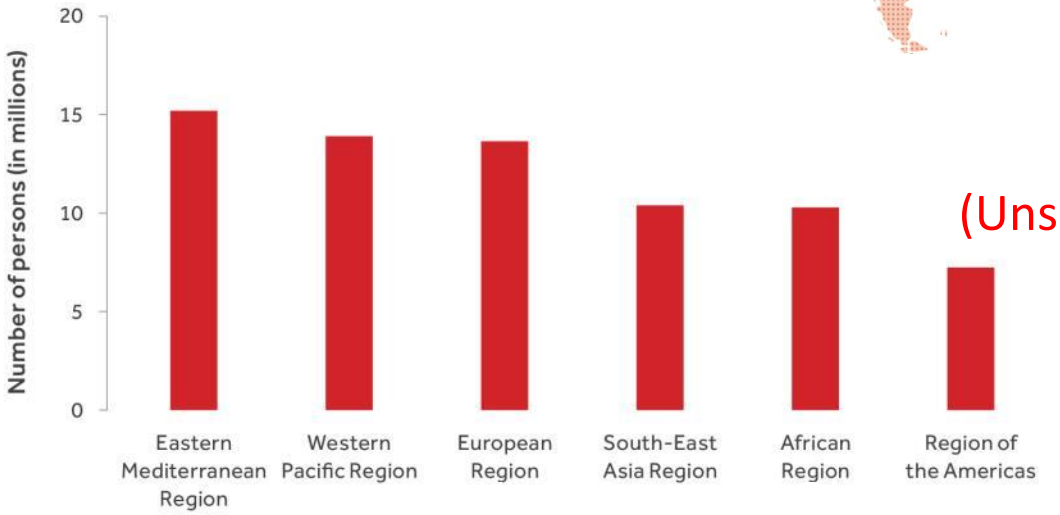
STATUS OF HEPATITIS C

HCV



Prevalence:

71 million infected, all regions



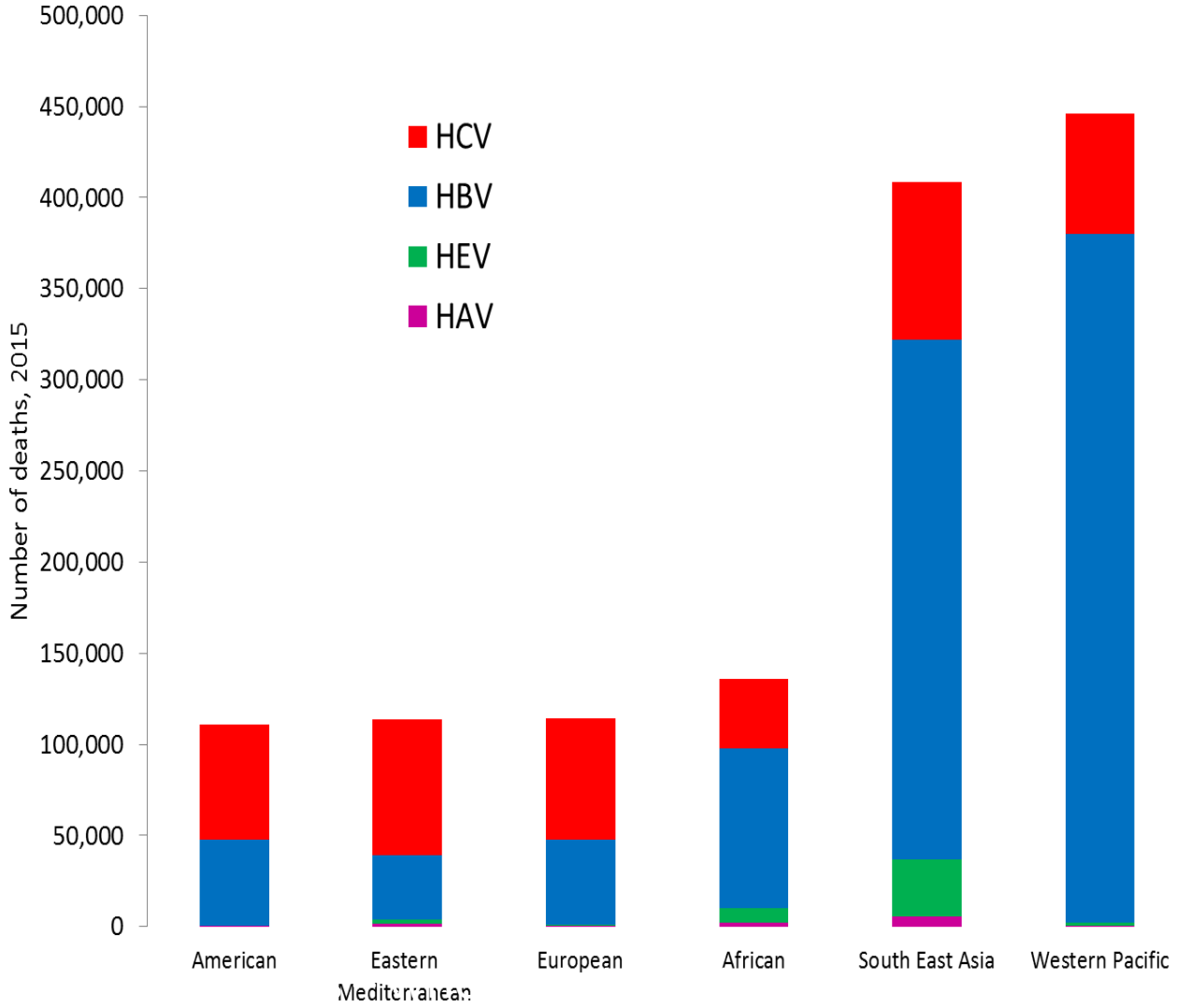
Incidence:

1.75 million new infections / year

(Unsafe health care and injection drug use)

HAV HEV HBV HCV

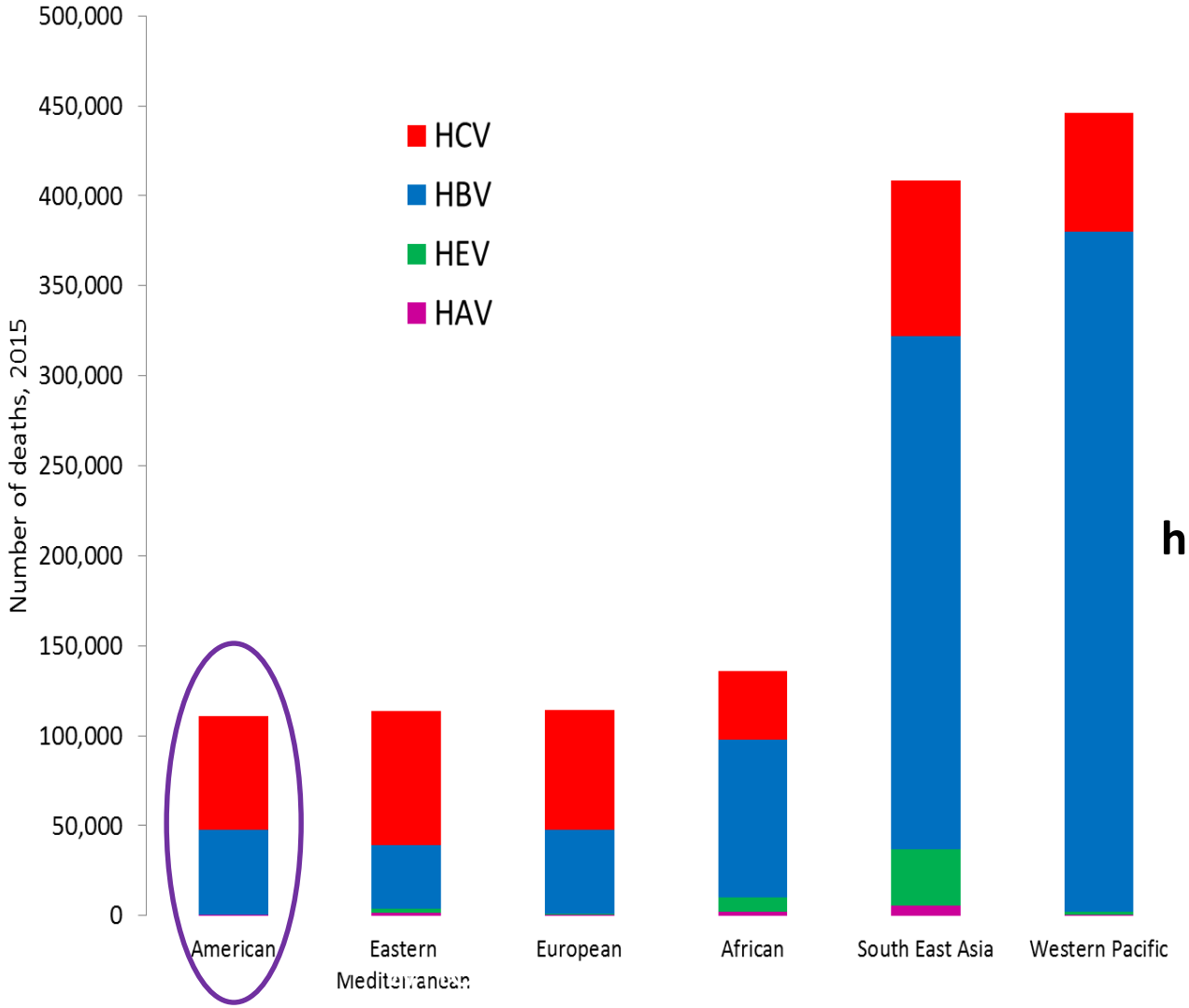
HEPATITIS DEATHS, BY VIRUS AND REGION, 2015



96% hepatitis deaths from HBV and HCV (cirrhosis and hepatocellular carcinoma)

HAV HEV HBV HCV

HEPATITIS DEATHS, BY VIRUS AND REGION, 2015



96% hepatitis deaths from HBV and HCV (cirrhosis and hepatocellular carcinoma)

RISK OF CIRRHOSIS AT 20 YEARS FOLLOWING INITIAL INFECTION

	Cumulated incidence of cirrhosis	Range
Cross sectional / retrospective	18%	15%-21%
Retrospective prospective studies	7%	4%-14%
Studies in non clinical setting	18%	16%-21%
All studies	16%	14%-19%

THEIN, H. H., YI, Q., DORE, G. J. & KRAHN, M. D. 2008. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology,* 48**,** 418-31.

Systematic review, Thein, Hepatology, 2008

BEYOND SVR:
IMPACT OF TREATMENT ON HEALTH OUTCOME

	HCV treatment OR	SVR OR
Hepatocellular carcinoma	0.392	0.203
Liver related mortality	0.363	0.126
All cause mortality	0.38	0.255

- No presentation stratified by initial fibrosis
- Patients with long term follow up tend to be patients with fibrosis treated with interferon rather than patients without fibrosis treated with direct acting anti-virals

*BANG, C. S. & SONG, I. H. 2017. Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. *BMC Gastroenterol,* 17**,** 46.

*WHO HCV treatment guidelines 2018 systematic review working group

2016 HCV guidelines remained complicated

Persons without cirrhosis

	Daclatasvir/ sofosbuvir	Ledipasvir/ sofosbuvir	Sofosbuvir/ ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

Persons with cirrhosis

	Daclatasvir/ sofosbuvir	Daclatasvir/ sofosbuvir/ ribavirin	Ledipasvir/ sofosbuvir	Ledipasvir/ sofosbuvir / ribavirin	Sofosbuvir/ ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

Treat all people with HCV infection

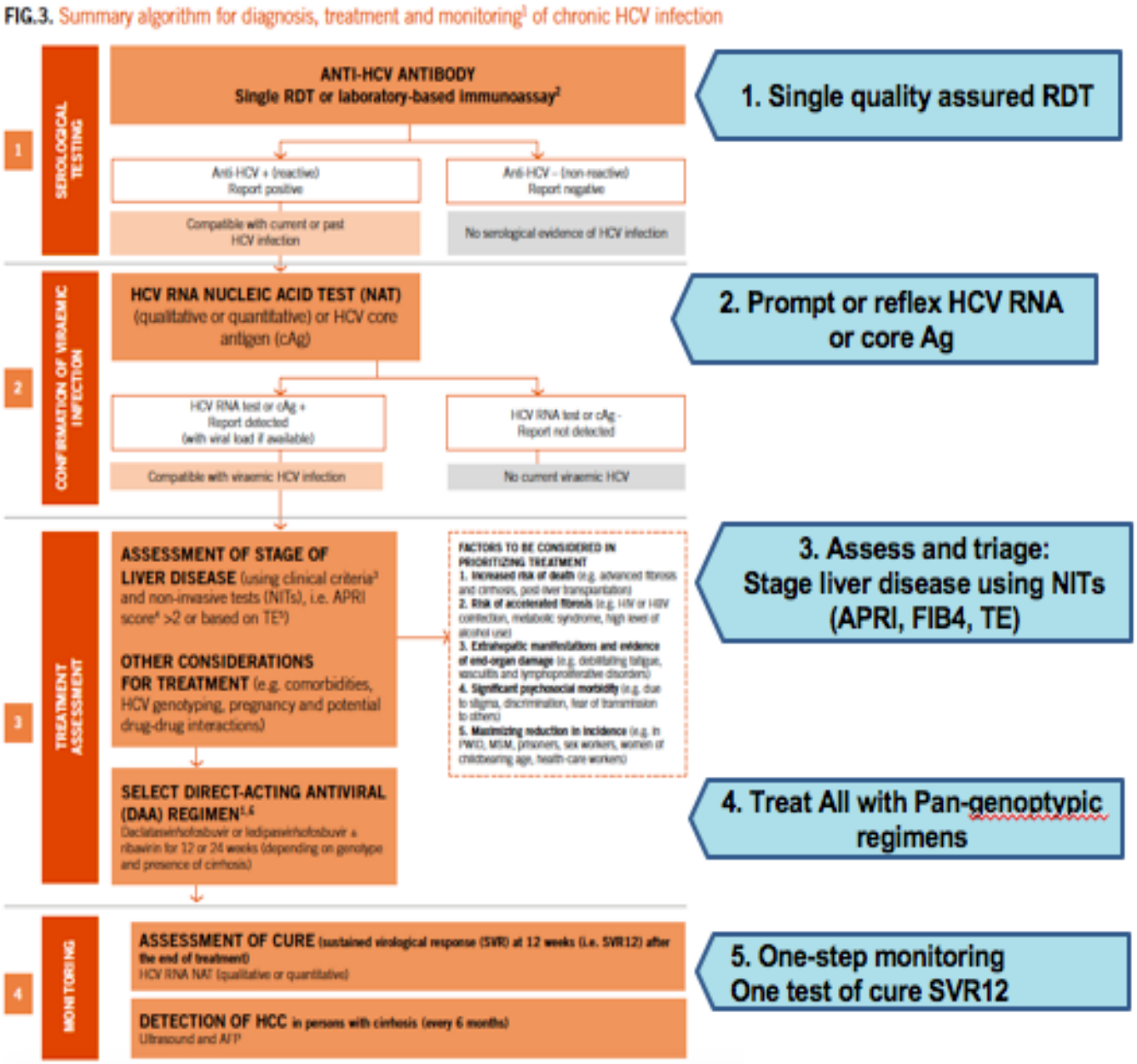
- WHO recommends offering **treatment to all** individuals diagnosed with HCV infection who are 12 years of age or older , irrespective of disease stage. (Strong recommendation, moderate quality of evidence)

- WHO recommends to **use pan-genotypic DAA** regimens for the treatment of persons with chronic HCV infection aged 18 years and above (conditional recommendation, moderate quality of evidence).

HCV treatment duration & availability

	Duration of treatment		Availability of product		
	Non cirrhotics (F0 – 3)	**Cirrhotic (F4)**	**Originator**	**'Access'**	**Generic**
Sofosbuvir/ Velpatasvir	12w	12w	yes	yes	no
Sofosbuvir/ Daclatasvir	12w	12 – 24w	yes	no	no
Glecaprevir/ Pibrentasvir	8w	12w	No	No	No

Simplified testing and management algorithms



Five key steps

ISSUES RELEVANT TO 'TREAT ALL': SYSTEMATIC REVIEWS

- No randomized control trials
- Risk of cirrhosis following initial infection
- Impact of treatment for patients with early fibrosis
- Safety of treatment
- Extra-hepatic manifestations
  - Prevalence
  - Effectiveness of treatment
- Public health impact of treatment as prevention
- Cost effectiveness

8 point approach to service delivery for treat all with pangenotypic regimens

1. Comprehensive **national planning** **for the elimination** of hepatitis C infection.
2. **Simple and standardized** **algorithms** across the continuum of care.
3. Strategies to **strengthen** **linkage** from testing to care, treatment and prevention
4. **Integration** of hepatitis testing, care and treatment with other services
5. **Decentralized** **services**, including task- sharing
6. C**ommunity** **engagement** and peer support to address stigma and discrimination
7. **Efficient** **procurement** **and supply management** of medicines and diagnostics
8. **Data systems** **to monitor** the quality of individual care and the cascade of care

Specific public health approaches in 5 population groups

- These population groups experience **high incidence or prevalence, stigma, discrimination, criminalization or special vulnerability.**
  - Persons who inject drugs
  - Persons in prisons or other closed settings
  - Men who have sex with men
  - Sex workers
  - Indigenous populations

HEPATITIS B TREATMENT

Ideal scenario

Curative treatment

+

Highly effective vaccine

Hepatitis B

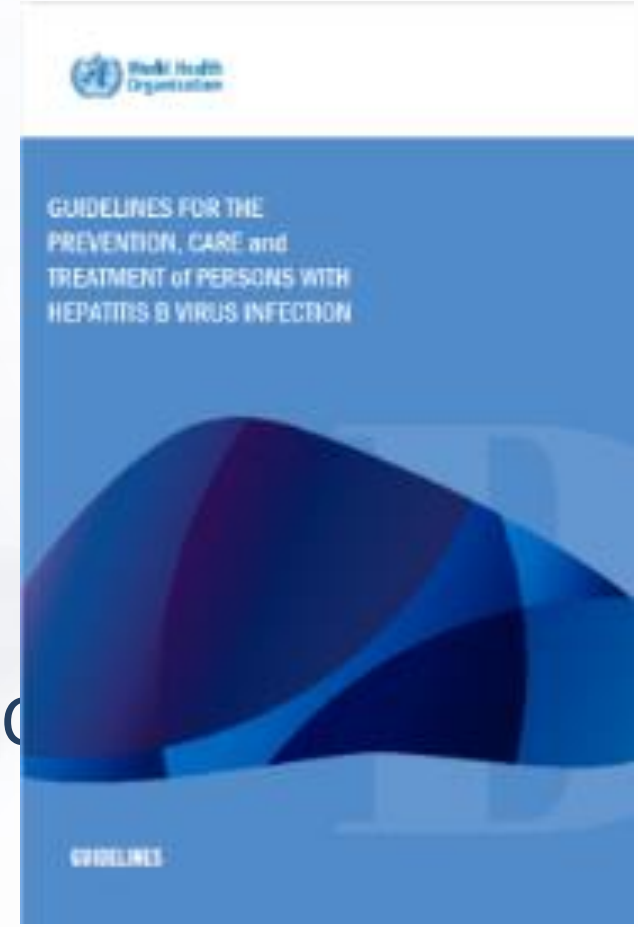
Effective, non-curative treatment

Vaccine - cheap, safe & effective

Treatment is relatively inexpensive, but lifelong

WHO Hepatitis B treatment guidelines 2015

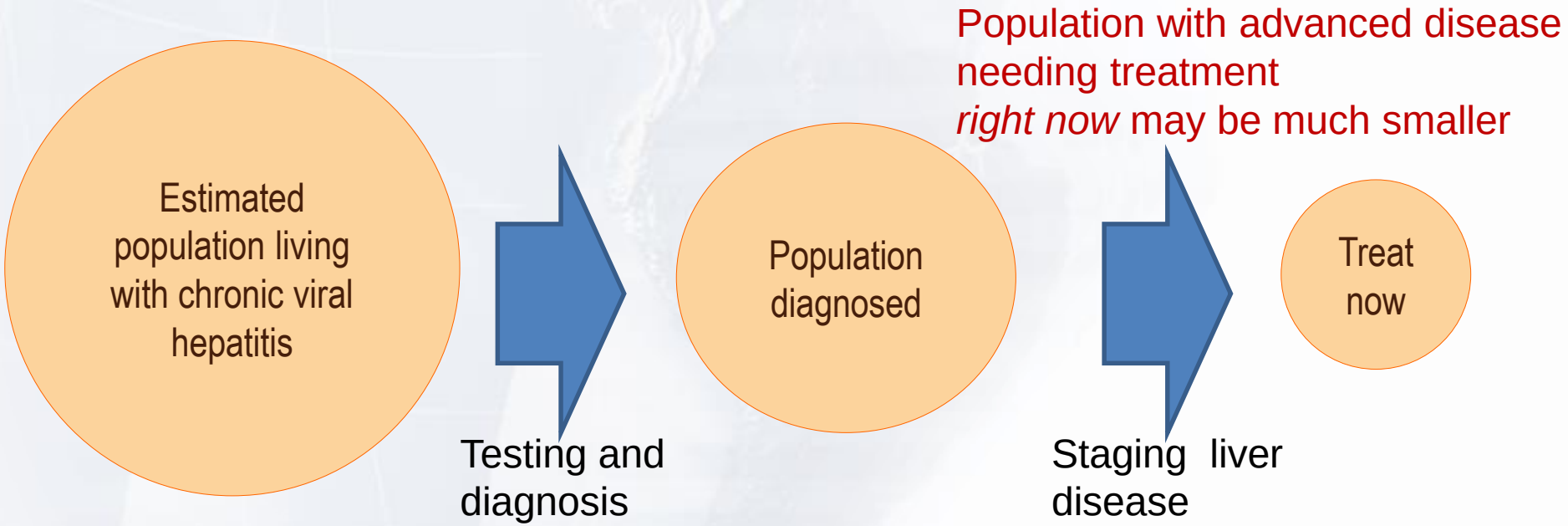
- Key recommendations and rationale
  - Use of NITs for **staging** of liver disease
  - **Who to treat**?
  - **What treatment** to use? (First and Second-Line)
  - How to **Monitor**? (ART, toxicity, HCC
  - **When to stop**?
  - Prevention
- Implementation considerations



Prioritizing treatment for those that need it most

- Mortality in chronic viral hepatitis is from cirrhosis and liver cancer

- STAGING disease prioritizes patients with advanced liver disease or treatment, given limited resources.



REVEAL-HBV cohort: Incidence of hepatocellular carcinoma

Participant characteristic	Incidence rate (x 100.000 Person-Years)	Adjusted RR (95%CI)
Gender		
Female	178	Ref
Male	530	3.0 (2.0 – 4.5)
Age		
30-39	111	Ref
40-49	399	3.6 (2.0 – 6.4)
50-59	566	5.1 (2.0 – 8.9)
>60	901	8.3 (4.6 – 15.0)
Baseline HBV DNA (copies/ml)		
<300	108	Ref
300 – 9999	111	NS
10000 – 99999	297	2.7 (1.3 – 5.6)
100000 – 999999	962	8.9 (4.6 – 17.5)
>1 million	1152	10.7 (5.7 – 20.1)
Baseline ALT (U/l)		
<45	337	Ref
>45	1342	4.1 (2.8 – 6.0)
HBeAg serostatus		
HBeAg -	264	Ref
HBeAg +	1130	4.3 (3.2 – 5.9)

Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. J Am Med Assoc. 2006;295(1):65–73.

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Age			
30-39	111	Ref	
40-49	399	3.6 (2.0 – 6.4)	
50-59	566	5.1 (2.0 – 8.9)	Older
>60	901	8.3 (4.6 – 15.0)	
Baseline HBV DNA (copies/ml)			
<300	108	Ref	
300 – 9999	111	NS	
10000 – 99999	297	2.7 (1.3 – 5.6)	
100000 – 999999	962	8.9 (4.6 – 17.5)	High VL
>1 million	1152	10.7 (5.7 – 20.1)	
Baseline ALT (U/l)			
<45	337	Ref	
>45	1342	4.1 (2.8 – 6.0)	High ALT

Progression of liver disease

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Non- invasive tests (NITs) to assess for cirrhosis

- Important for decisions on prioritising who needs treatment
- Liver biopsy considered impracticable in low income settings

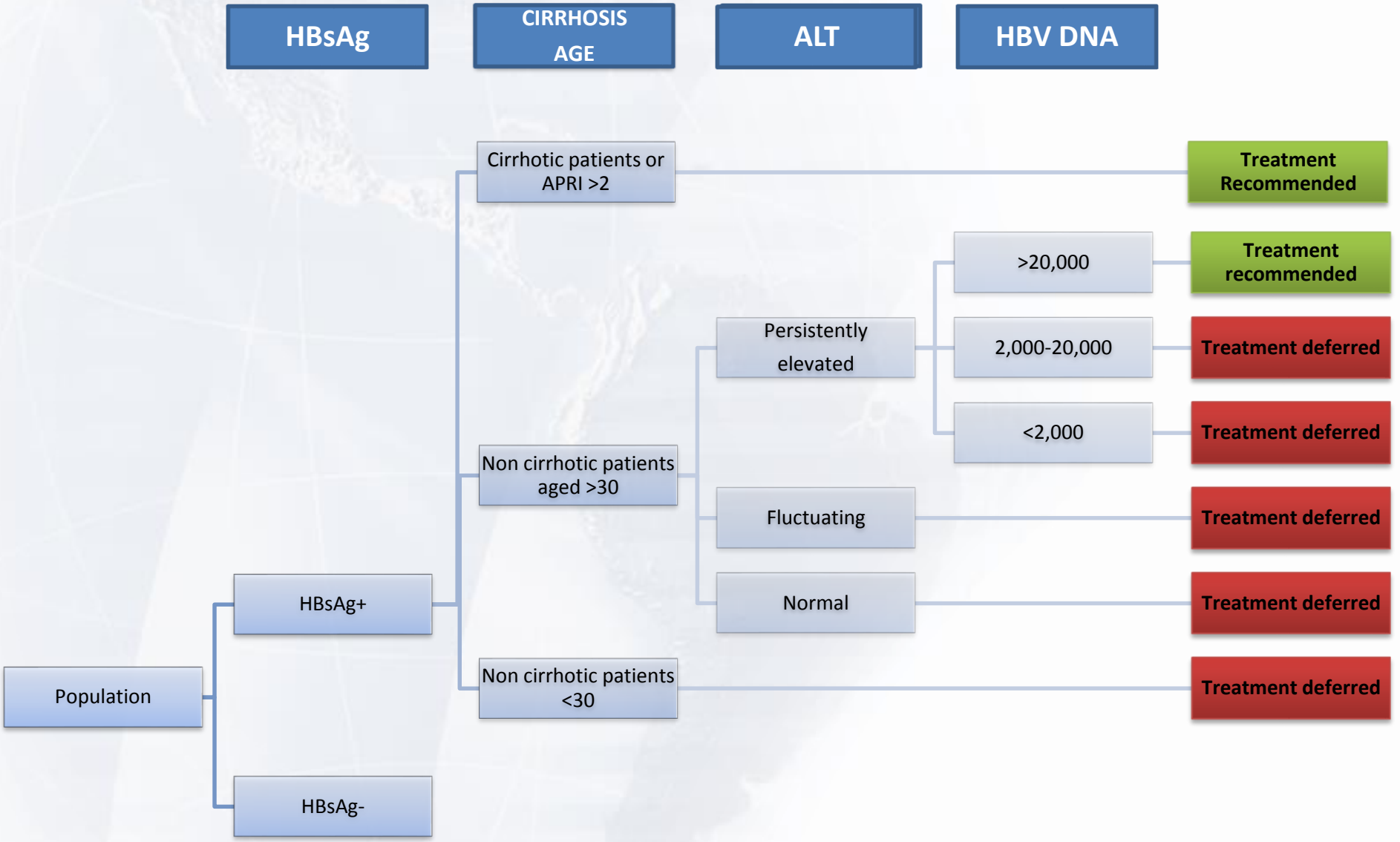
APRI	AST, platelets
FIB-4	Age, AST, ALT, platelets
FibroTest	5 serum markers
FibroScan	Transient elastography

RECOMMENDATION	STRENGTH	EVIDENCE QUALITY
▪ **APRI is the preferred NIT** to assess for presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. ▪ Transient elastography or FibroTest may preferred NIT in settings where they are available and cost is not a major constraint.	Conditional	Low

HBV antiviral treatment

- In adults and those > 12 years, nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (**tenofovir or entecavir**) are recommended. *(Strong recommendation, moderate quality of evidence)*
  - NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended. (*Strong recommendation, moderate quality of evidence*)
  - persons with confirmed or suspected antiviral resistance, a switch to tenofovir is recommended. (*Strong recommendation, low quality of evidence*)

Hepatitis B treatment decision tree

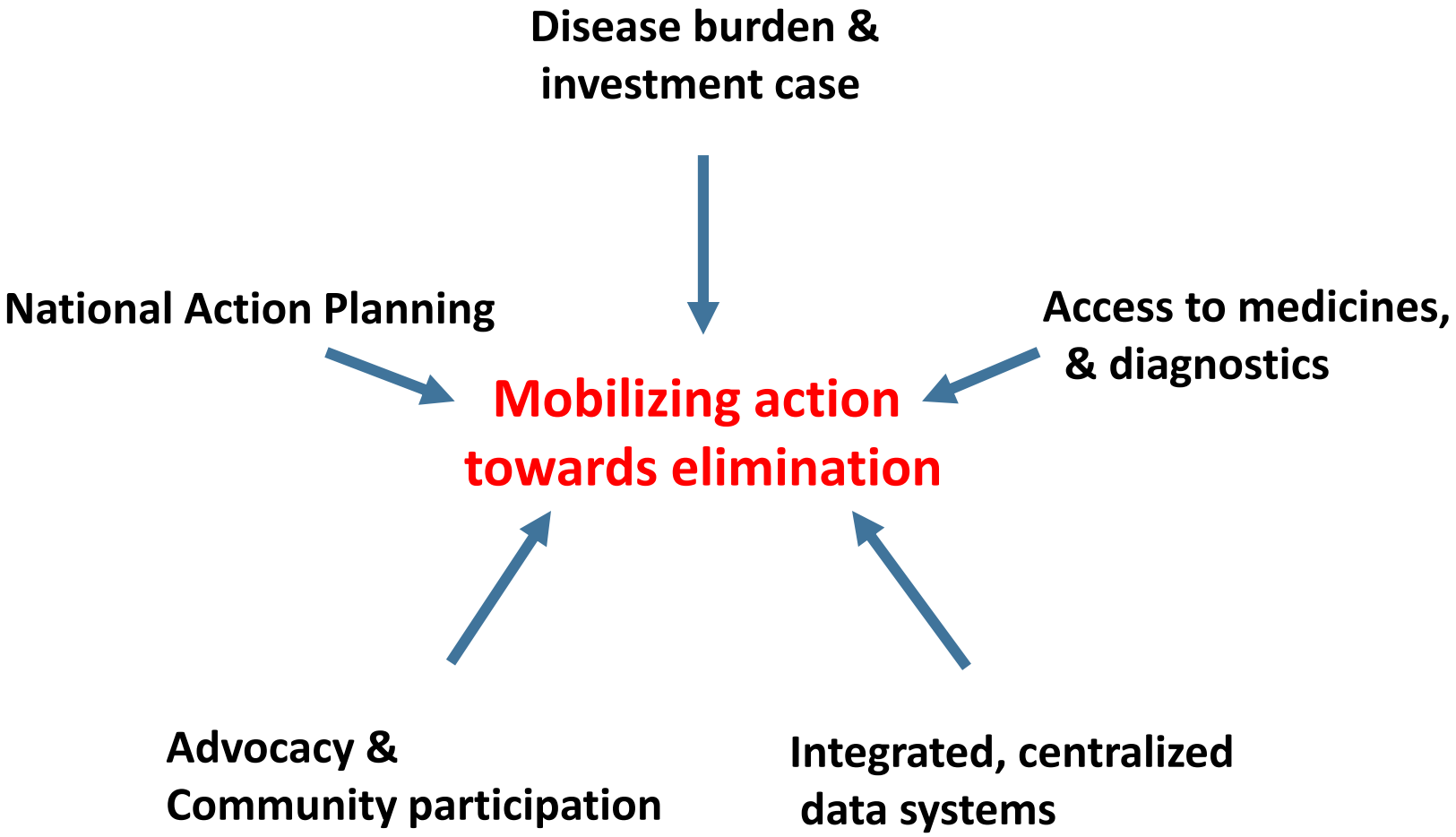


Conclusion

- Hepatitis treatment is cancer prevention
- The burden of hepatitis in the Caribbean for HBV > HCV
- Treatment is not possible without diagnosis
- Prices are continuing to reduce
- PAHO stands ready to support action to increase the availability of diagnosis and treatment in the Caribbean

QUESTIONS, COMMENTS

PAHO's Comprehensive support to address hepatitis



The utility of the investment case for hepatitis

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Pan American Health Organization

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OFICINA REGIONAL PARA LAS Américas

The challenge facing hepatitis

- Funders increasingly **prioritizing** to cope with **fewer resources** and **more goals**.
- Hepatitis programmes need to know:
  - Domestic resource mobilization?
  - External donor funding?
  - Innovative financing mechanisms?

Integration = sustainability

- The core of sustainable financing is a programme optimized in cost and impact.
- Benefit from lessons learned with HIV/AIDS and avoid:
  - off-budget, parallel systems, or
  - separate delivery and financing arrangements.
- It is necessary to understand the key aspects of services (who benefits, how organized) and design finance accordingly.

Possible responses?

- Disease-specific approaches:
  - earmarked taxes (like in tobacco control)?
  - dedicated funding sources (like GFATM)?
- But, let's consider the lessons of these experiences:
  - **sustainability** is not just about **revenue**,
  - **purchasing, pooling** and **delivery** must be efficient too.

The UHC lens: our only alternative

The unit of analysis is the health system:

- Develop the financing strategy at the sectoral level, not for “hepatitis” only.
- Formulate goals at population level, not just for hepatitis programme beneficiaries.

- On health financing: can priority interventions be integrated into benefit packages and purchasing arrangements?
  - Can hepatitis be the disease that solves a health system problem?
- Beyond health financing: will not strong, unified support systems also serve priority interventions?
  - Think IT, procurement…

The investment case

- The investment case is a strategic decision making tools to inform the most effective and cost-efficient policy suite to address hepatitis…i.e.:

What is the public health and economic impact of population level interventions to address hepatitis in a country

Process of disease burden and economic analysis

Disease burden estimates

- Disease progression model, transmission models for HBV/HCV (either or both)
- Prevalence estimates over time (to 2030)
- Liver related disease (LRD) outcomes over time - cirrhosis, HCC and deaths

Intervention scenarios:

- ***Comparing public health impacts* of different population level treatment strategies***
- Baseline (no interventions)
- Status quo (no further intervention)
- Reduce mortality objective
- Elimination objective

Cost Estimation

- **Direct costs** (all healthcare costs such as diagnosis, staging, and hospitalisation associated with management of infection and sequelae)
- **Indirect costs** (lost productivity and life expectancy), measured in DALY/VSLY
- **Cost of antiviral therapies** (current practice vs. new DAAs/recommended therapies)

CEA

- current practice vs standardized care and treatment package
- old (if applicable) vs new antivirals
- price points for cost saving for new medicines

Budget Impact

- Direct and antiviral costs over time

Financing Strategies

- **Who will pay? Payment scenarios involving stakeholders**:
  - Govt vs health insurance vs individual
  - Combination scenarios
  - Co-payment estimations (only where applicable)

Cost Sensitivity

- Sensitivity analysis to identify uncertaintaies in cost inputs

Our investment case work so far

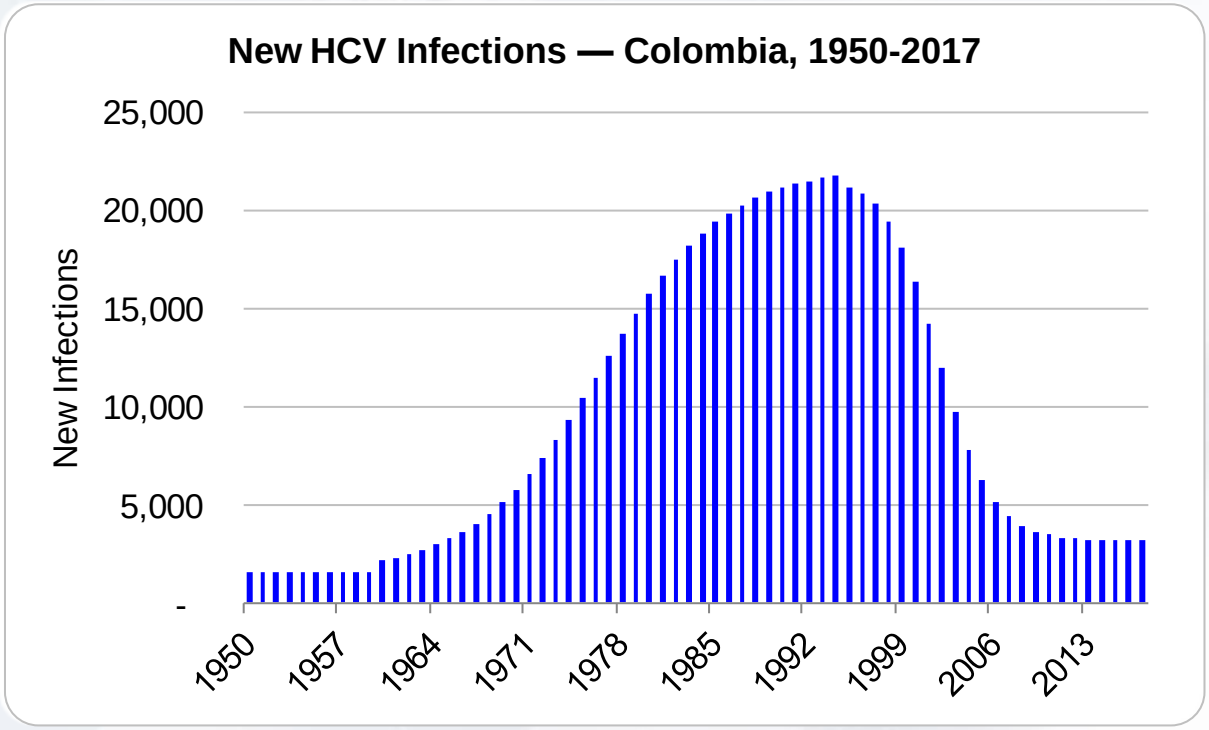
- Brazil (HBV, HCV)
- Colombia (HCV)
- Chile, Argentina (HCV) ongoing
- No countries of the Caribbean or Central America
- Not all countries need an investment case, especially where burden is very low

EXAMPLES…ILLUSTRATIVE ONLY

HEPATITIS C

Incidence (back calculated from prevalence)

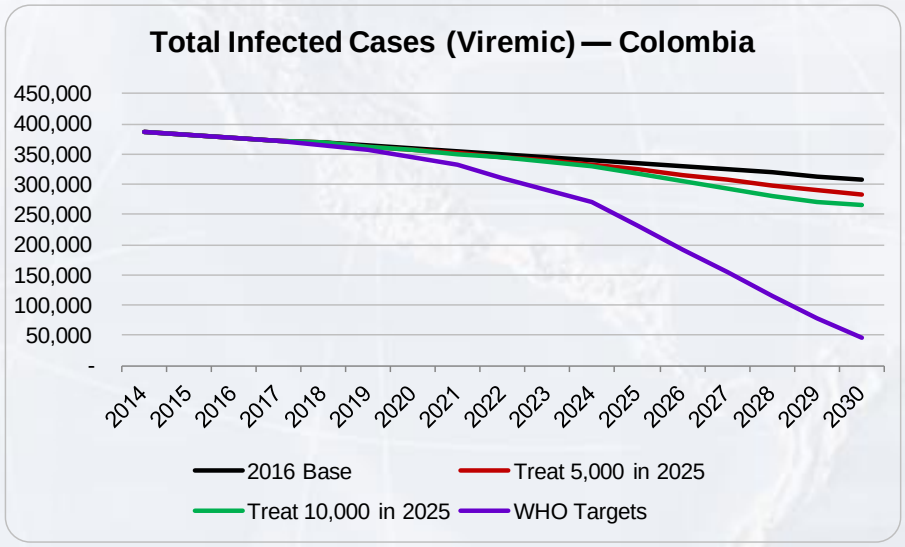
$$Prevalence_{\,Year\ x} = \sum_{t=1950}^{x} (Incidence_t - \mathrm{Mortality_t} - \mathrm{Cured_t})$$

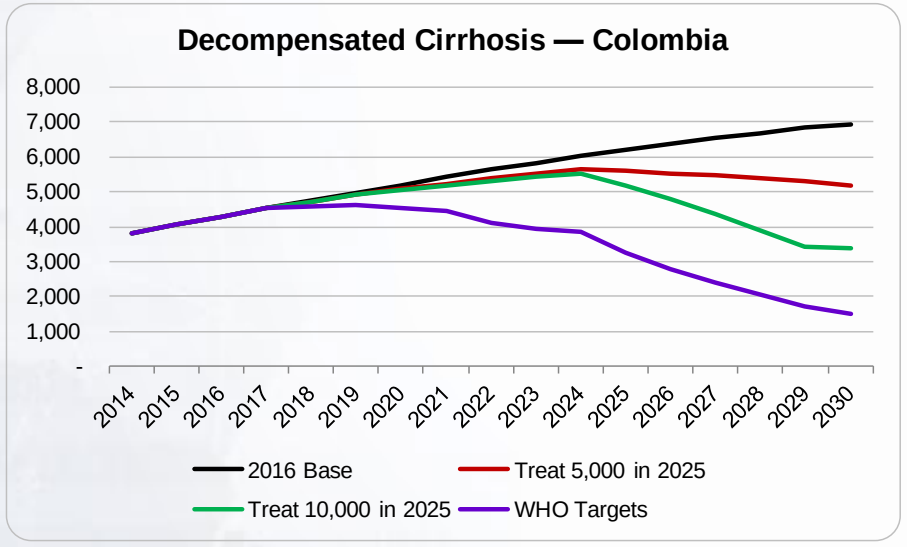


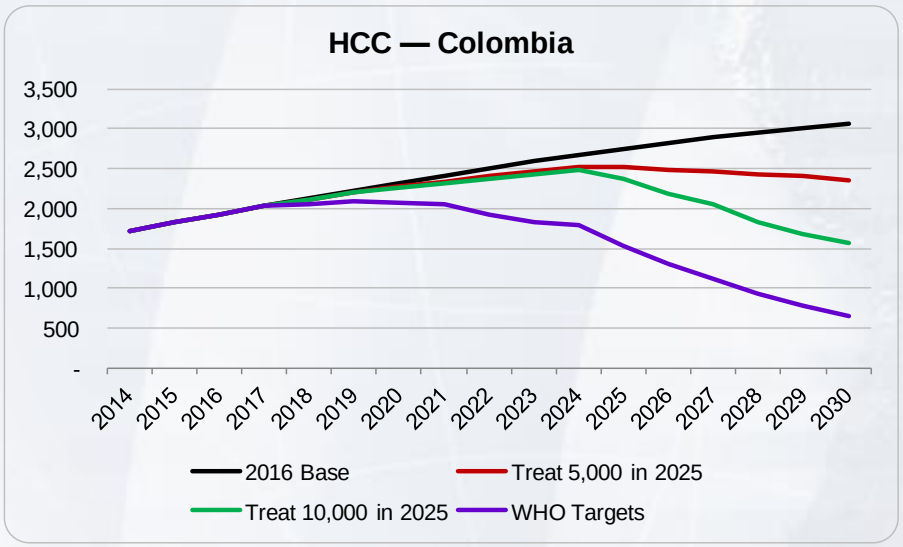
Key determinant: when national blood donor screening commenced.

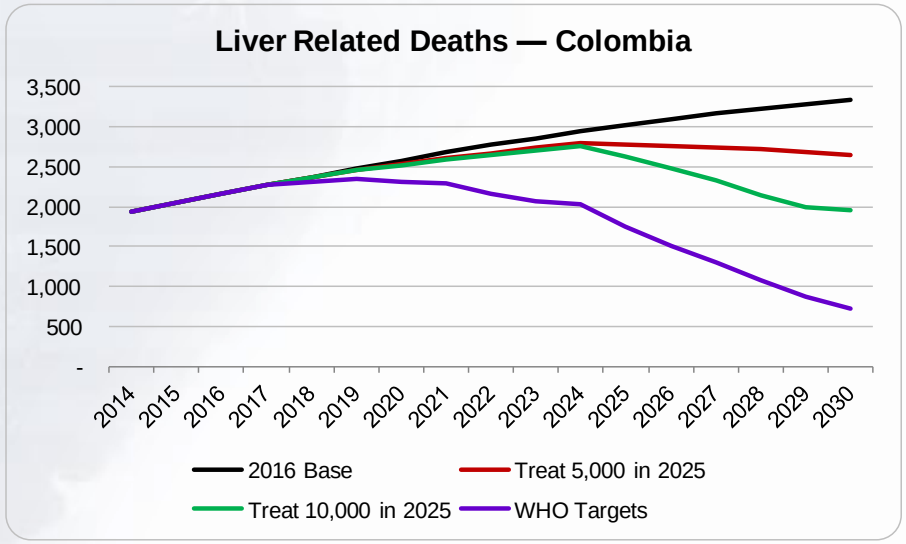
In 2016, an estimated 3200 new infections occurred

Impact of different strategies on prevalence, HCV related liver disease and deaths

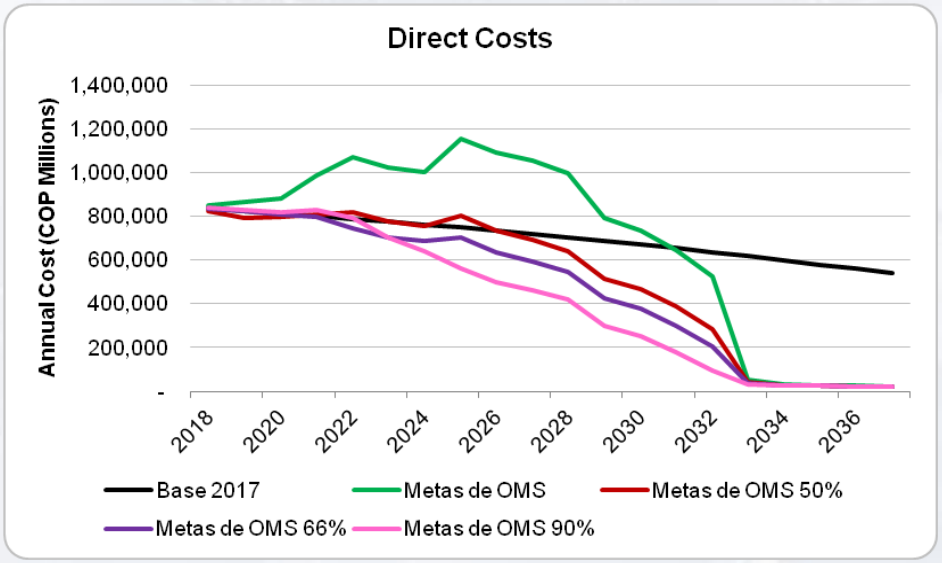


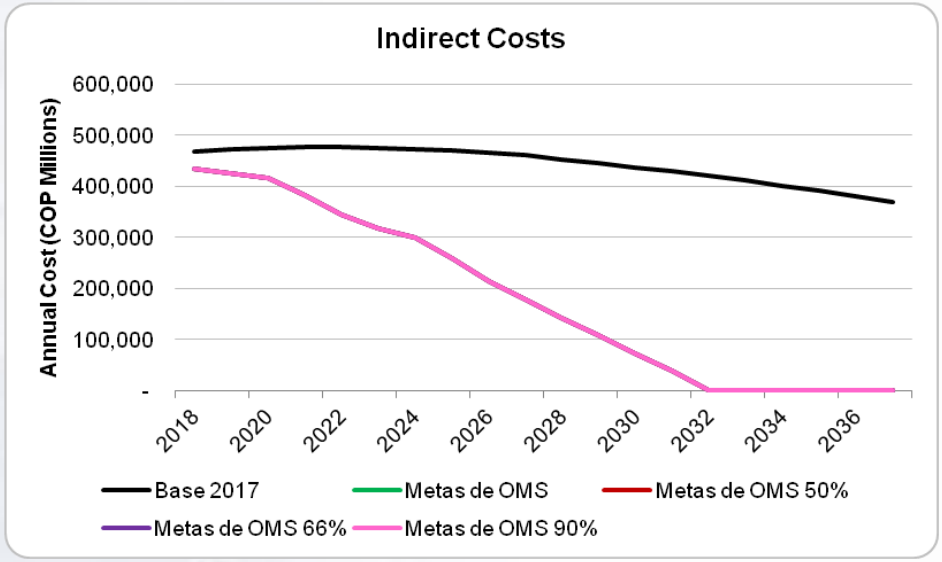


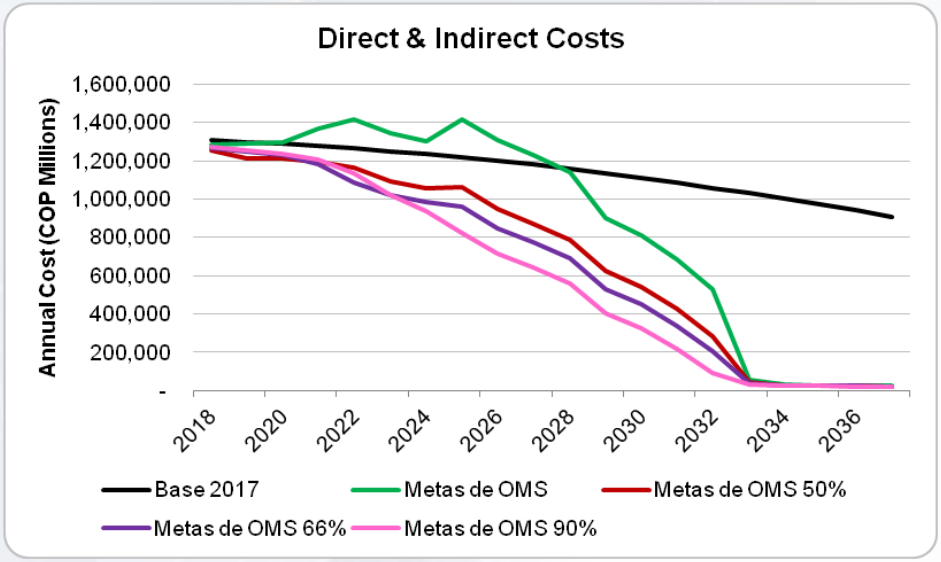




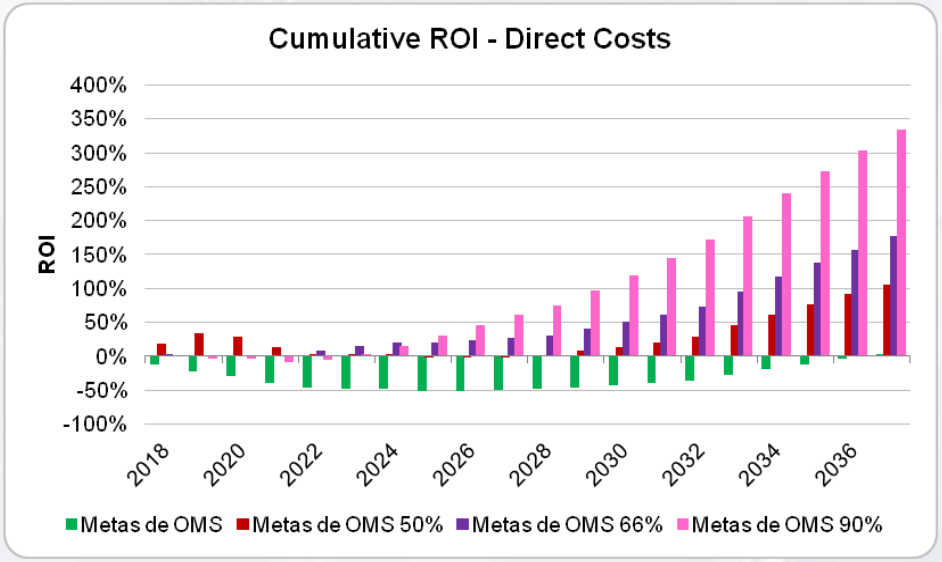
The upfront investment can be decreased by lower diagnosis and treatment prices as shown in the elimination scenario

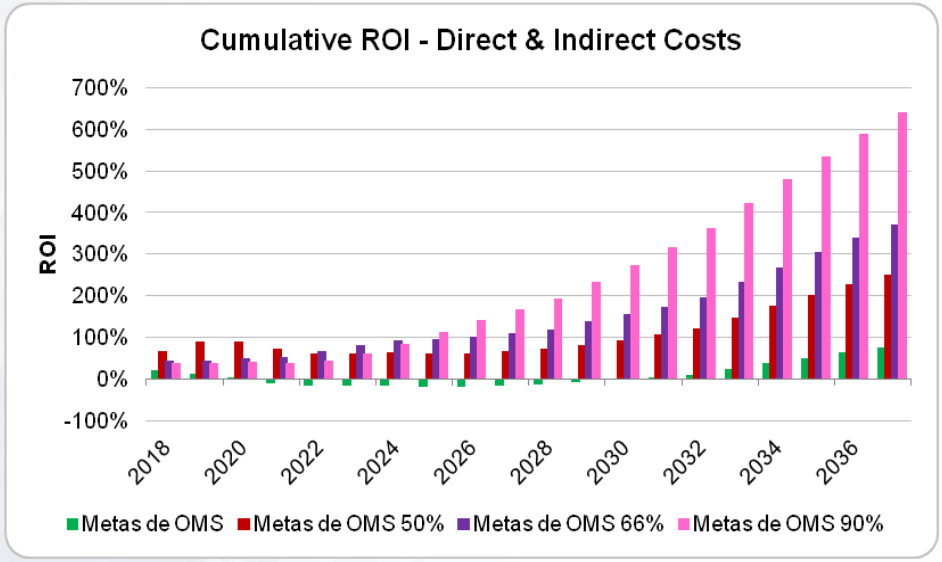


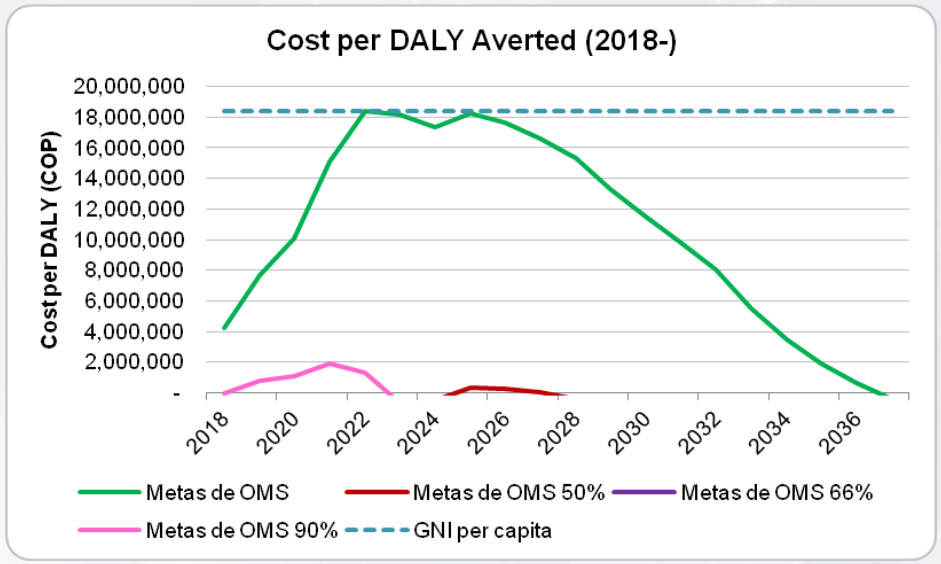


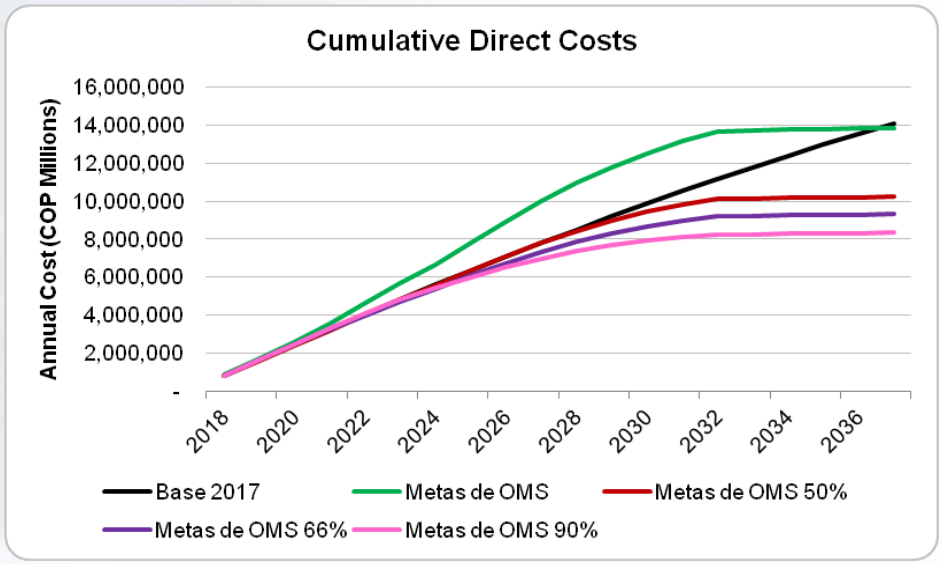


Elimination is the most cost-effective scenario





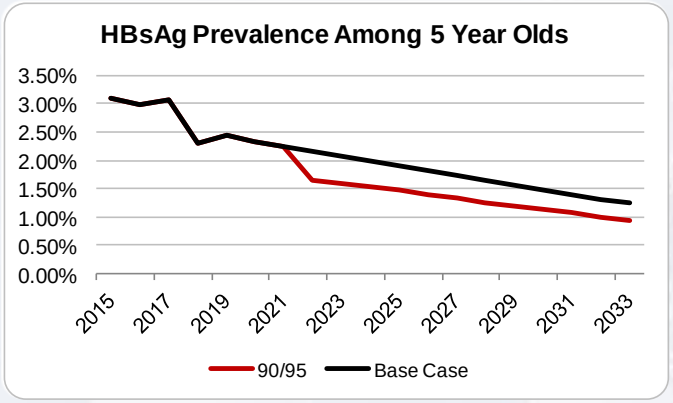


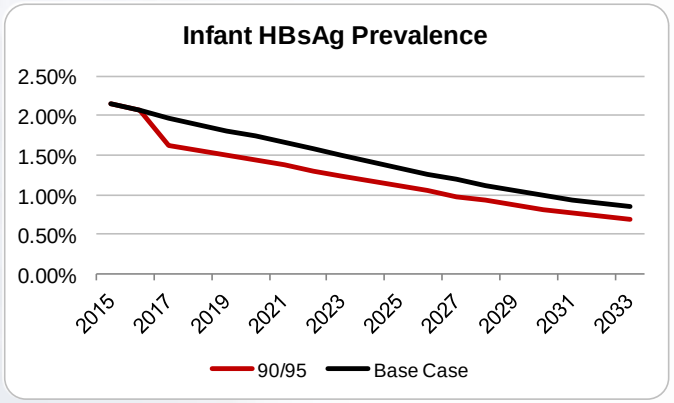


HEPATITIS B

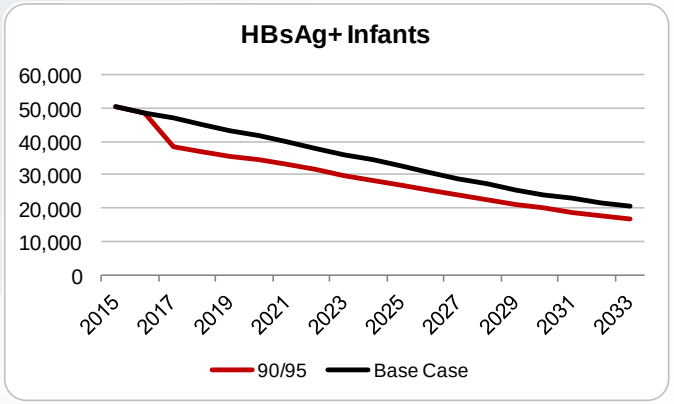
Increasing birth dose (BD) vaccination to 90% and 3 dose (3D) vaccination to 95% starting in 2017 will reduce incidence

- Based on the current perinatal prophylaxes coverage of 54% birth dose and 79% coverage of three doses it is estimated that the HBsAg+ prevalence among 5-year olds will reach 1.0% in 2036
- By increasing birth dose coverage to 90% and three dose coverage to 95% in 2017, the target of 1.0% is estimated to be reached in 2032

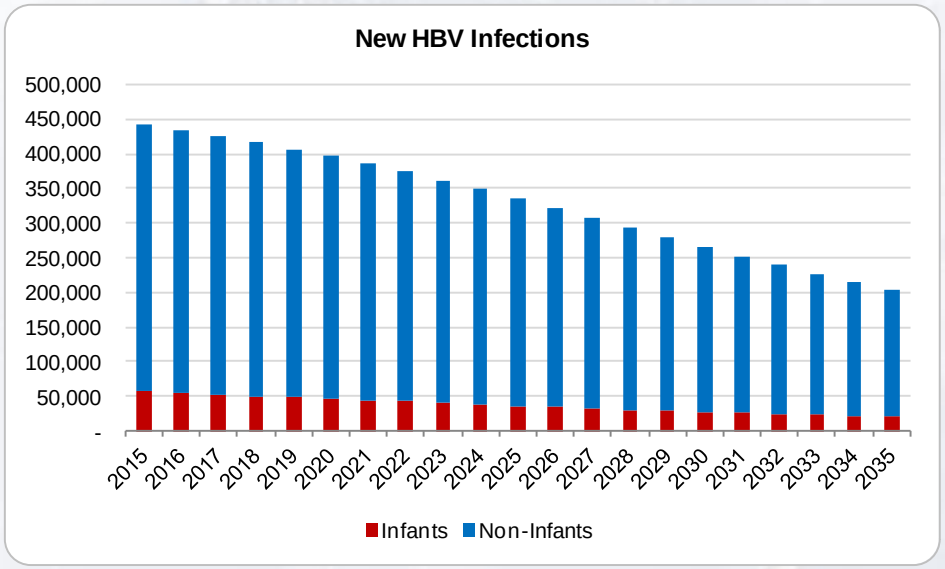




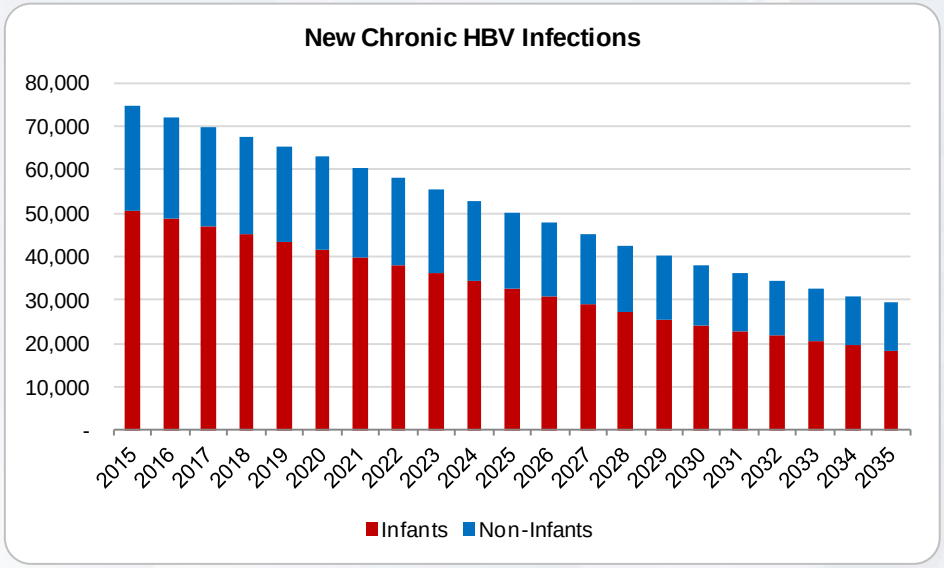
Increased vaccination will also reduce incidence among infants. Between 2017-2033, 100,000 new infections will be averted.

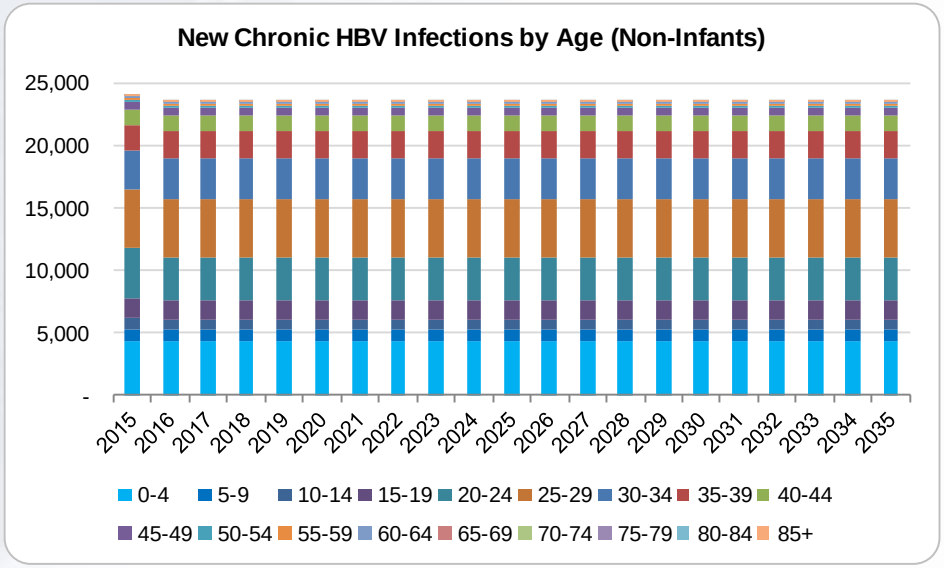


Most acute infections occur among adults but perinatal transmission remains a main risk factor for chronic infections

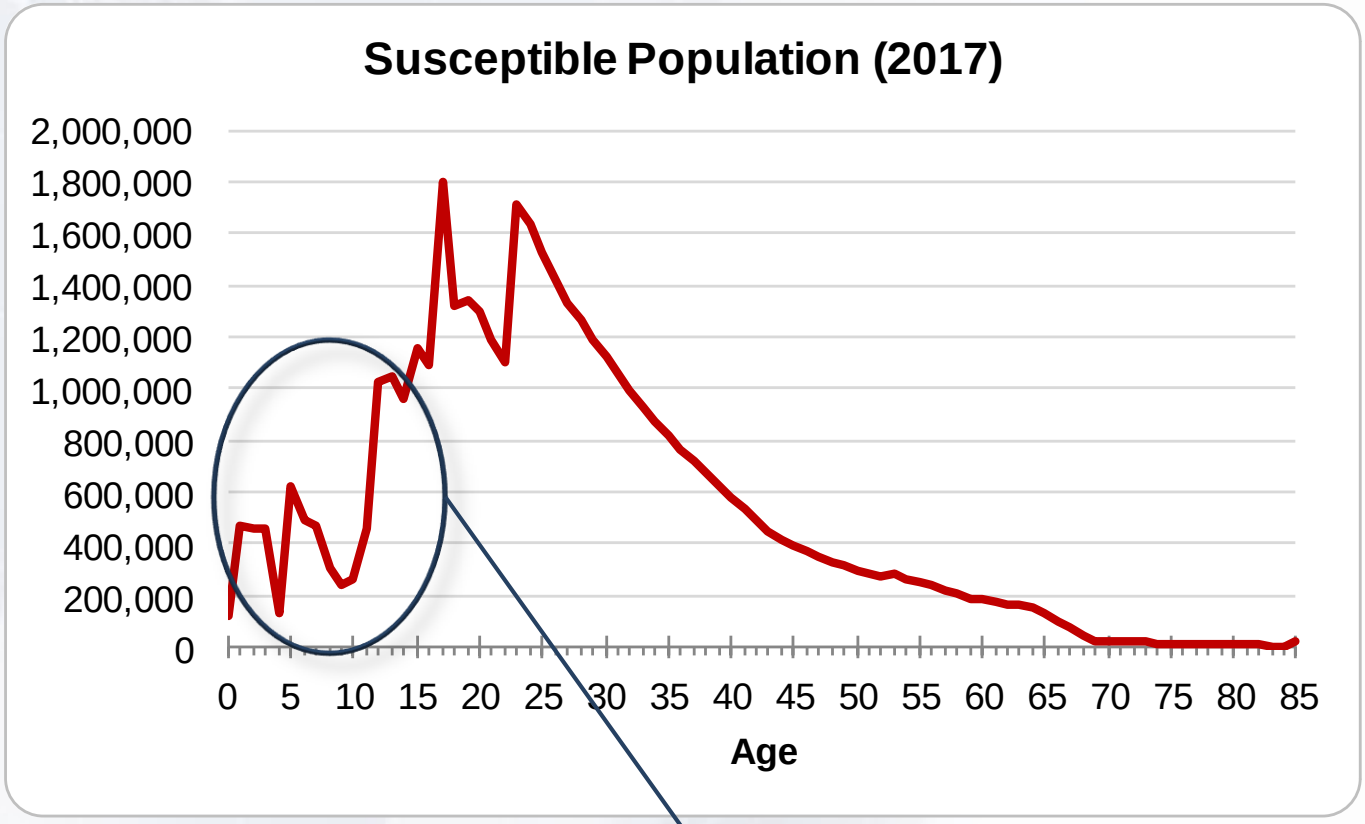


Among non-infants, most new infections are occurring after birth (0-4) and among those aged 20-34.



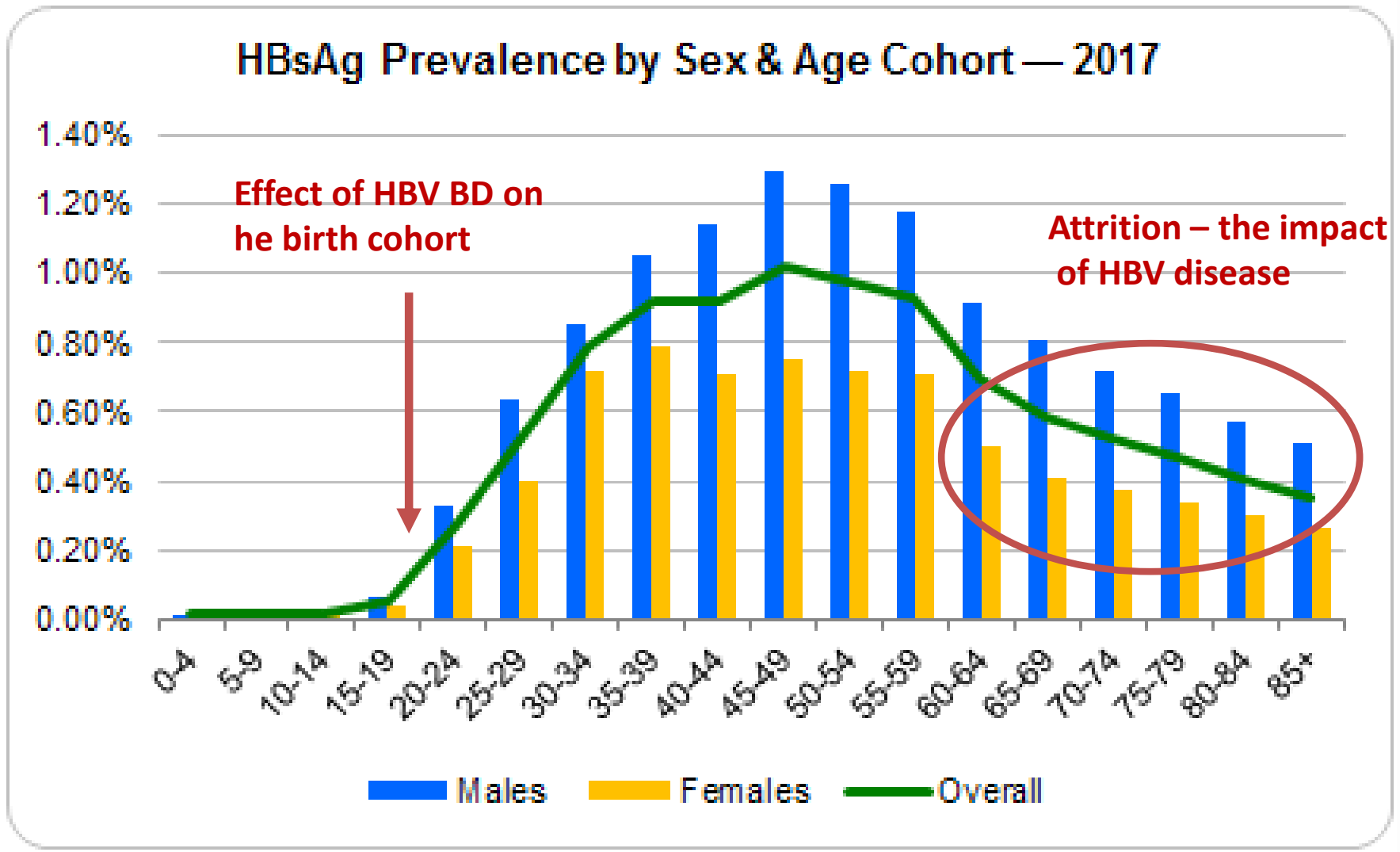


The cost of catch up vaccination will depend on the age group selected

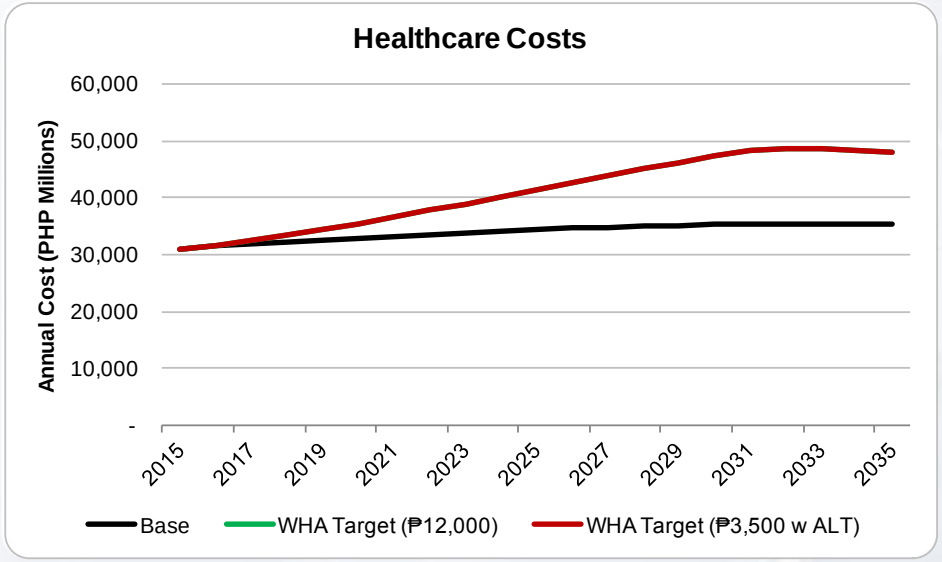


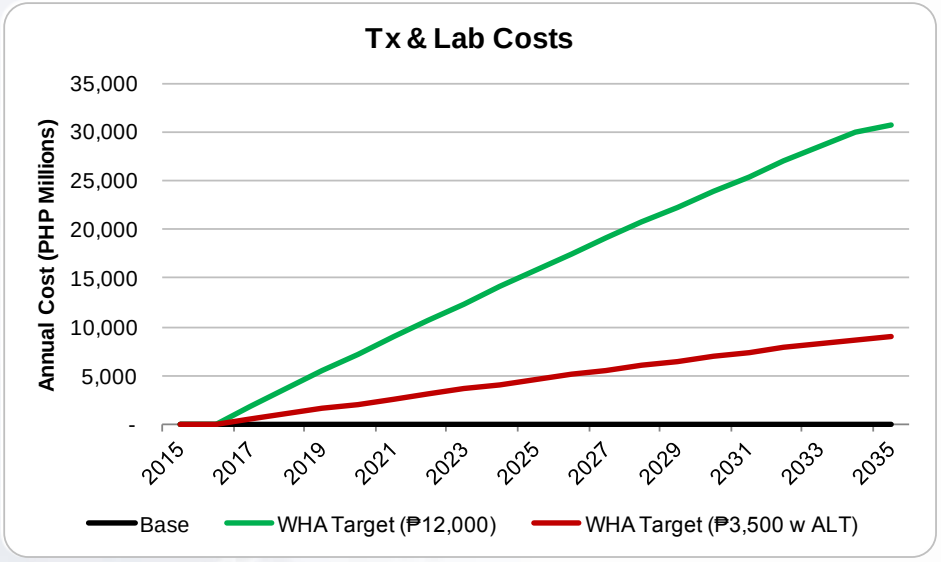
The pediatric population have a much higher rate of progression to chronic HBV. There are 11.4 million susceptible to infection (1-17 years old), but vaccination of this population will require testing for core antigen first.

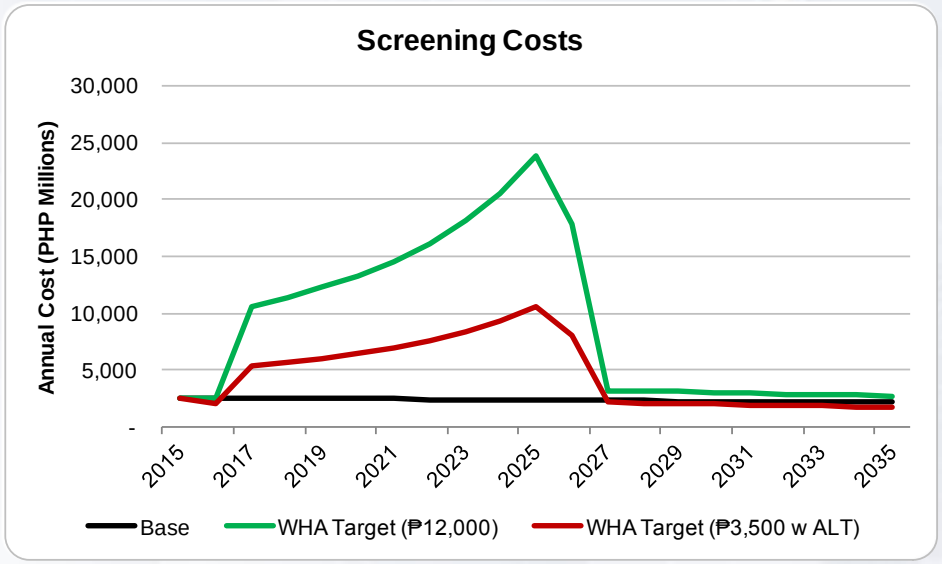
HBsAg+ Prevalence by Age

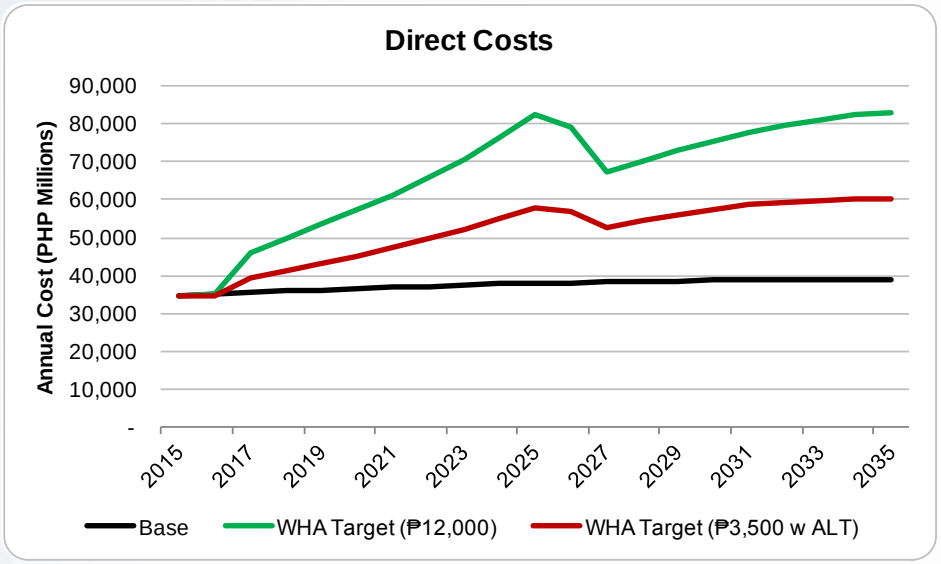


Healthcare costs will increase as more patients are diagnosed & require follow up. Drug pricing has a large impact on total spending.









Conclusions

- The investment case for hepatitis is a valuable strategic planning tool that carries weight in policy decision making
- Ideally, it is carried out in conjunction with
  - National Action Plan development
  - Increased access to diagnostics & medicines
  - Normative guidance development

QUESTIONS, COMMENTS