The WHO Congenital Syphilis Estimation Tool: Structure and Methods
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Glossary

ABO	Adverse Birth Outcome
ANC	Antenatal Care
BPG	Benzathine Benzylpenicillin
CS	Congenital Syphilis
GAM	WHO Global Aids Monitoring Database
LBW	Low Birth Weight
RPR	Rapid Plasma Reagin
SNTTP	Serology Non-Treponemal and Treponema Pallidum
The Tool	The WHO Congenital Syphilis Estimation Tool
TPHA	Treponema Pallidum Hemagglutination Assay
TPPA	Treponema Pallidum Particle Agglutination Assay
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization

1. Background

The WHO Congenital Syphilis (CS) Estimation Tool (the Tool) (https://www.who.int/reproductivehealth/congenital-syphilis/surveillance/en) was developed as a tool for countries to estimate current and historical CS case numbers, case rates and adverse birth outcomes (ABOs) and to look at future trends in CS cases under different scenarios of antenatal care (ANC) coverage and maternal syphilis testing and treatment. It can also be used to estimate benzathine benzylpenicillin (BPG) requirements for maternal syphilis treatment (1 dose of 2.4 million units of BPG per seropositive woman). The Tool builds on the methods used by World Health Organization (WHO) to estimate global CSs (Korenromp et al., 2019; Newman et al., 2013; Wijesooriya et al., 2016).

2. Model structure

2.1. Classification of the population

Figure S 1 gives an overview of the Tool's structure. The Tool divided pregnant women into seven categories based on whether or not they attended ANC, their true syphilis status, and whether they were tested and/ or treated for syphilis:

1) $T_{t,c}^{1A}$: the number of pregnant women testing positive and treated who are true positives;
2) $T_{t,c}^{1B}$: the number of pregnant women testing positive and treated who are *not* true positives;
3) $T_{t,c}^{2A}$: the number of pregnant women testing positive but *not* treated who are true positives;
4) $T_{t,c}^{2B}$: the number of pregnant women testing positive but *not* treated who are *not* true positives;
5) $T_{t,c}^{3A}$: the number of pregnant women *not* attending ANC who are true positives;
6) $T_{t,c}^{3B}$: the number of pregnant women *not* attending ANC who are *not* true positives;
7) $T_{t,c}^{4}$: the number of pregnant women who are syphilis negative;

for a country, *c*, and a year, *t*. The population was divided as such in order to (a) facilitate estimation of the number of tests administered (b) allow adjustment of the syphilis prevalence using the test-type correction factor (see Figure S 1). The number of women in each category was calculated as follows:

$$T_{t,c}^{1A} = \rho_{t,c}\, N_{t,c}\, \alpha_{t,c}\, \beta_{t,c}\, \mu_{t,c}\, C_{t,c} \quad (1)$$

$$T_{t,c}^{1B} = \rho_{t,c}\, N_{t,c}\, \alpha_{t,c}\, \beta_{t,c}\, \mu_{t,c}\, (1 - C_{t,c}) \quad (2)$$

$$T_{t,c}^{2A} = \rho_{t,c}\, N_{t,c}\, \alpha_{t,c}\, \beta_{t,c}\, (1 - \mu_{t,c})\, C_{t,c} \quad (3)$$

$$T_{t,c}^{2B} = \rho_{t,c}\, N_{t,c}\, \alpha_{t,c}\, \beta_{t,c}\, (1 - \mu_{t,c})\, (1 - C_{t,c}) \quad (4)$$

$$T_{t,c}^{3A} = \rho_{t,c}\, N_{t,c}\big[[\alpha_{t,c}\, (1 - \beta_{t,c})\, C_{t,c}] + [(1 - \alpha_{t,c})C_{t,c}]\big] \quad (5)$$

$$T_{t,c}^{3B} = \rho_{t,c}\, N_{t,c}\, \big[[\alpha_{t,c}\, (1 - \beta_{t,c})(1 - C_{t,c})] + [(1 - \alpha_{t,c})(1 - C_{t,c})]\big] \quad (6)$$

$$T_{t,c}^{4} = \big(1 - \rho_{t,c}\big)N_{t,c} \quad (7)$$

where $\rho_{t,c}$ is syphilis prevalence, $N_{t,c}$ is the number of live births, $\alpha_{t,c}$ is the ANC coverage, $\beta_{t,c}$ is testing coverage, $\mu_{t,c}$ is treatment coverage and $C_{t,c}$ is the test type correction for a year, *t*, and country, *c*.

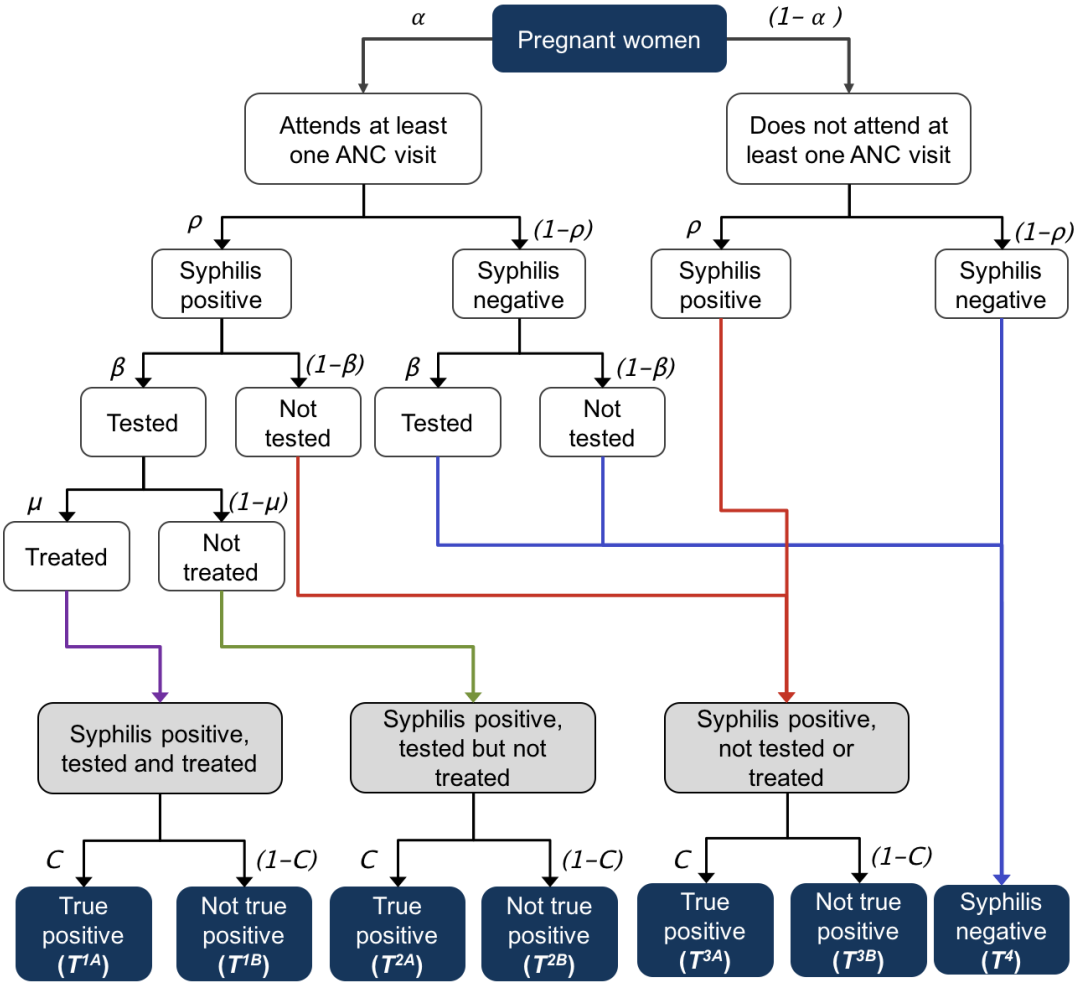

Figure S 1. Diagrammatic representation of the structure of the tool. Parameter α is the ANC coverage rate; ρ is the syphilis prevalence; β is the syphilis testing rate; μ is the syphilis treatment rate; C is the test-type correction factor.

2.2. ABOs in untreated women

Categories $T_{t,c}^{1A}, \ldots, T_{t,c}^{4}$ (equations 1-7) were combined with ABO risks (see

Table S *1*) to estimate the number of ABOs. The 6×1 matrix $\boldsymbol{\delta}_{t,c}^{NT}$ holds the case numbers of five ABOs and the number of normal births for a year, *t,* and country, *c*, in untreated, seropositive women, calculated as follows:

$$\boldsymbol{\delta}_{t,c}^{NT} = \begin{bmatrix} Normal\ births \\ Surveillance\ cases \\ Stillbirths \\ Neonatal\ deaths \\ Premature\ /\ LBW \\ Clinical\ CS \end{bmatrix} = \begin{bmatrix} 0 \\ 1-(R^{NT1}+,\ldots,+R^{NT4}) \\ R^{NT1} \\ R^{NT2} \\ R^{NT3} \\ R^{NT4} \end{bmatrix} \left[T_{t,c}^{2A} + T_{t,c}^{3A}\right] \quad (8)$$

2.3. Gestational week of first treatment and ABO risk

The average gestational week of first ANC visit and the national level ABO risk were estimated using the methods described in (Korenromp et al., 2019). The average gestational week of first ANC visit was used as a proxy for the timing of first testing and treatment, *ω(t,c),* for a year, *t*, and a country, *c*. A scaling factor, $\eta_{t,c}$, was used to scale ABO risk (see

Table S *1*) to reflect the time of first treatment, *ω(t,c)*. $\eta_{t,c}$ was estimated by fitting an exponential function to the data in Korenromp et al. (2019) using non-linear least-squares regression:

$$\eta_{t,c} = e^{(a+b\ \omega_{t,c})} \quad (9)$$

where *a* and *b* are constants. All regression analyses were carried out using R version 3.2 (R Core Team, 2018). Estimated parameters were *a = -2.59* and *b=0.11*. The resulting scaling factor, $\eta_{t,c}$, reflects the proportion of the average ABO risk (8.3%, see **Error! Reference source not found.**) incurred in a country as a function of average gestational week of treatment.

2.4. ABOs in treated women

For treated seropositive women, $\boldsymbol{\delta}_{t,c}^{T}$, for a year, *t*, and country, *c*, ABOs were calculated as follows.

$$\boldsymbol{\delta}_{t,c}^{T} = \begin{bmatrix} Normal\ births \\ Surveillance\ cases \\ Stillbirths \\ Neonatal\ deaths \\ Premature\ /\ LBW \\ Clinical\ CS \end{bmatrix} = \eta_{t,c} \begin{bmatrix} 1-(R^{T1}+,\ldots,+R^{T4}) \\ 0 \\ R^{T1} \\ R^{T2} \\ R^{T3} \\ R^{T4} \end{bmatrix} \left[T_{t,c}^{1A}\right] \quad (10)$$

2.5. Total CS cases

The birth outcomes for all seropositive mothers irrespective of treatment status, $\Delta_{t,c}$, in a given year, *t*, and country, *c*, were calculated as follows:

$$\Delta_{t,c} = \boldsymbol{\delta}_{t,c}^{NT} + \boldsymbol{\delta}_{t,c}^{T} \quad (11)$$

These case numbers were extracted for each ABO and totaled to give the total number of CS cases, $CS_{t,c}$, for a year, *t,* and a country, *c*.

CS cases include both clinical congenital syphilis cases (symptomatic at birth) and surveillance cases (by the WHO definition) (World Health Organization, 2017). All infants born to untreated women are

considered to be surveillance cases irrespective of whether or not an ABO occurs. Infants born to treated mothers are not considered CS cases unless they are symptomatic at birth or have an ABO.

2.6. User input and tool projection

The Tool iterated Equations 1-11 for $t = 2012,\ldots,2030$ to generate annual case rate estimates by country, c and uses the most recent available data to calculate the case rates for the present year. When generating future estimates, The Tool implicitly assumed that prevalence remained constant over time. Users, however, were able to enter target coverage rates for ANC, testing and treatment coverage and a target year for when these coverage levels will be reached. Coverage rates were scaled up linearly on an annual basis to ensure the coverage rate was achieved by the target year. For example, if the 2019 ANC coverage was 10% and the user specified a target of 90% by 2027 then annual ANC coverage, $\alpha_{t,c}$, would bve increased by 10% each year.

$$\alpha_{t,c} = \begin{cases} \alpha_{t-1,c} + \frac{\alpha_T - \alpha_{2019,c}}{t_T - 2019} & if\ \alpha_{t-1,c} \neq \alpha_T\ and\ t > t^* \\ \alpha_{t-1,c} & if\ \alpha_{t-1,c} = \alpha_T\ and\ t > t^* \end{cases} \quad (12)$$

where α_T is the target ANC coverage rate, t_T is the target year and t^* is the current year. The same approach is applied for testing coverage, $\beta_{t,c}$, and treatment coverage, $\mu_{t,c}$.

3. Model parameters

3.1. Syphilis test-type correction

The Tool applied a test-type correction factor ($C_{t,c}$) to reflect that, depending on the diagnostic test used, a positive test results may not indicate active syphilis. As in previous WHO estimates true active syphilis case is defined as concurrent positivity on both a non-treponemal (e.g., Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test and a treponemal test (e.g., TPHA or SNTTP). This means that no correction was applied to prevalence estimates based on both a treponemal and non-treponemal test. However when only a non-treponemal test was used the correction factor was set at 52.2%, when only a treponemal test was used the correction factor was set a 53.6% and when no test type was reported the correction factor was set at 68.6% (Ham et al., 2015).

3.2. Adverse birth outcomes

The probability of developing an ABO (stillbirth, neonatal death, prematurity, low birth weight (LBW) and clinical CS) were determined from relevant systematic reviews (see Table S1) (Blencowe et al., 2011; Gomez et al., 2013) and the work by Qin et al. (2014) and Hawkes et al. (2013), which suggested maternal treatment is more effective the earlier a woman is treated during a pregnancy (Hawkes et al., 2013; Qin et al., 2014). The risk in treated women of developing a particular ABO was calculated as follows:

$$Risk\ in\ treated\ women = (1 - reduction\ in\ risk) \cdot (risk\ in\ untreated\ women) \quad (13)$$

Table S 1. Risk of ABOs in untreated and treated women. Within the Tool, the ABO risks shown in this table were scaled by the national average week of first treatment, according to section 2.3. *The WHO surveillance definition includes all infants born to untreated women.

Birth outcome	**Risk in untreated women (Gomez et al., 2013)**	**Reduction in risk after treatment (Blencowe et al., 2011)**	**Risk in adequately treated women (from equation 13)**
Total ABO risk	52.0%	-	8.3%
Clinical CS	16.0%	97.0%	0.5%
Premature / LBW	6.0%	64.0%	2.2%
Stillbirth	21.0%	82.0%	3.8%
Neonatal death	9.0%	80.0%	1.8%
Surveillance case without ABO	48.0%	-	0.0%
Total CS risk	100.0%*	-	8.3%
Normal birth	0.0%	-	91.7%

4. Country specific parameters

Table S *2* summarizes each of the country specific parameters, the preloaded values and potential data sources. The majority of pre-loaded data come from the WHO Global Aids Monitoring database (GAM). It should be noted, that the GAM data are country provided data and there are some inconsistencies in the data due to limited reporting and variable case definitions.

Table S 2. Overview of country specific parameters, the preloaded data and other potential data sources that could be used. The Tool also includes a functionality where users can override pre-loaded data and use their own data for all input parameters.

Symbol	Parameter	Definition	Preloaded data	Other potential data sources
$N_{t,c}$	Number of pregnant women		Annual live births between 2003 and 2030 were sourced from the United Nations Population Division (UNPD).	Data are currently sparse; the number of live births was used as a surrogate measure
$\rho_{t,c}$	Syphilis prevalence in pregnant women		GAM; derived by dividing the reported number of pregnant women testing positive for by the reported number of pregnant women tested as the denominator.	- In-country ANC surveillance - Published studies - Spectrum-STI
$\alpha_{t,c}$	ANC coverage	Proportion attending at least one antenatal care visit	GAM; derived by dividing the reported number of women attending ANC by the number of pregnant women (see above).	- In-country ANC surveillance - Published studies
$\beta_{t,c}$	Testing coverage	Proportion attending ANC screened for syphilis	GAM; derived by dividing the reported number of women tested by the reported number of women attending ANC.	- In-country ANC surveillance - Published studies
$\mu_{t,c}$	Treatment coverage	The proportion of syphilis positive women treated effectively	GAM; derived by dividing the reported number of women treated by the reported number of women tested.	- In-country ANC surveillance - Published studies
$\omega_{t,c}$	Gestational week of first treatment		Derived according to (Korenromp et al., 2019)	In-country ANC surveillance
$C_{t,c}$	CS cases		GAM	In-country CS case reporting

5. References

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