Estimating Benzathine Penicillin Need for the Treatment of Pregnant Women Diagnosed with Syphilis during Antenatal Care in High-Morbidity Countries

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Abstract

Background
Congenital syphilis continues to be a preventable cause of global stillbirth and neonatal morbidity and mortality. Shortages of injectable penicillin, the only recommended treatment for pregnant women and infants with syphilis, have been reported by high-morbidity countries. We sought to estimate current and projected annual needs for benzathine penicillin in antenatal care settings for 30 high syphilis burden countries that account for approximately 33% of the global burden of congenital syphilis.

Methods
Proportions of antenatal care attendance, syphilis screening coverage in pregnancy, syphilis prevalence among pregnant women, and adverse pregnancy outcomes due to untreated maternal syphilis reported to WHO were applied to 2012 birth estimates for 30 high syphilis burden countries to estimate current and projected benzathine penicillin need for prevention of congenital syphilis.

Results
Using current antenatal care syphilis screening coverage and seroprevalence, we estimated the total number of women requiring treatment with at least one injection of 2.4 MU of benzathine penicillin in these 30 countries to be 351,016. Syphilis screening coverage at or above 95% for all 30 countries would increase the number of women requiring treatment with benzathine penicillin to 712,030. Based on WHO management guidelines, 351,016 doses of weight-based benzathine penicillin would also be needed for the live-born infants of mothers who test positive and are treated for syphilis in pregnancy. Assuming availability of penicillin and provision of treatment for all mothers diagnosed with syphilis, an estimated
95,938 adverse birth outcomes overall would be prevented including 37,822 stillbirths,
15,814 neonatal deaths, and 34,088 other congenital syphilis cases.

Conclusion
Penicillin need for maternal and infant syphilis treatment is high among this group of syphilis
burdened countries. Initiatives to ensure a stable and adequate supply of benzathine peni-
cillin for treatment of maternal syphilis are important for congenital syphilis prevention, and
will be increasingly critical in the future as more countries move toward elimination targets.

Introduction
Syphilis infection can be transmitted from mother to infant during pregnancy resulting in con-
genital syphilis. Injectable penicillin is the only recommended treatment for syphilis occurring
in pregnant women to prevent congenital syphilis and for infants born with congenital syphilis
[1,2]. Maternal syphilis can result in adverse birth outcomes due to congenital syphilis in over
half of untreated pregnancies. These adverse birth outcomes include: prematurity/low-birth
weight, congenital deformities (neurological, bone, and organ damage), stillbirth, and neonatal
death [3]. Provided early in pregnancy, penicillin can prevent mother-to-child transmission of
syphilis and related adverse birth outcomes [4].

WHO has received reports of stock outs and shortages of injectable benzathine penicillin
from multiple countries, many with a high burden of maternal and congenital syphilis [5,6].
Benzathine penicillin, used to treat syphilis, is an older, generic, injectable medication that has
a limited manufacturing base. Each of these factors may reduce benzathine penicillin availabil-
ity. [7]. One injection of 2.4 million units of intramuscular benzathine penicillin is recom-
manded for pregnant women with early stage syphilis and three injections spaced by one week
apart are recommended for late or unknown stage syphilis [1]. Limited data is available on the
use of non-penicillin alternative therapies in pregnancy [2,8]. Azithromycin does not cross the
placenta in adequate amounts to treat a syphilis-infected foetus [9], and reports of adverse
birth outcomes due to congenital syphilis have been reported among pregnant women treated
for syphilis with azithromycin [10]. Syphilis treatment failure due to the emergence of azithro-
mycin resistance has been reported in some regions [2]. Ceftriaxone crosses the placental
barrier but the optimal dose and duration of therapy for pregnant women is unknown and dis-
placement of bilirubin from albumin-binding sites may increase the risk of kernicterus in new-
borns [8, 11]. Tetracyclines are contraindicated during pregnancy [2]. Concerns for untreated
or inadequately treated maternal syphilis resulting in adverse pregnancy outcomes call for
increased awareness and vigilance to ensure a stable supply of benzathine penicillin.

The World Health Organization (WHO) has established country targets for validation of
elimination of mother-to-child transmission of syphilis which include: (1) at least 95% of preg-
nant women attend antenatal care (ANC), (2) at least 95% of pregnant women receive syphilis
screening during ANC and (3) at least 95% of syphilis seropositive pregnant women receive
adequate treatment, defined as at least 2.4 mu intramuscular benzathine penicillin G [1, 12].
Increasing syphilis screening during antenatal care to achieve elimination targets will involve
increased demand for benzathine penicillin. We sought to estimate the current and projected
annual number of benzathine penicillin doses needed for pregnant women who test positive
for syphilis and their infants in 30 high-morbidity countries to help manufacturers and coun-
tries prepare for full scale antenatal syphilis screening and treatment programs.
Methods

In projecting global needs for injectable penicillin, we focused on the countries that accounted for a high number of congenital syphilis cases or have been identified by WHO as priority settings for congenital syphilis elimination [13]. We used Global AIDS Response Progress Reporting (GARPR) data [14,15] reported to WHO by countries on syphilis screening coverage and prevalence among pregnant women attending ANC.

Selection of the 30 high syphilis burden countries

The 12 high-burden countries identified as priority settings for elimination of congenital syphilis were included [13]. These 12 countries represent four WHO regions of Africa (Central African Republic, Ghana, Madagascar, Mozambique, Tanzania, Zambia), the Americas (Honduras, Uruguay), Western Asia and the Pacific (China, Papua New Guinea) and Southeast Asia (Indonesia, Myanmar). We also included data from 14 countries reporting ANC syphilis screening coverage of at least 10% and syphilis seroprevalence of at least 1% for GARPR reporting year 2014 (Argentina, Bolivia, Burkina Faso, Chad, Democratic Republic of Congo (DRC), Haiti, Kenya, Liberia, Mali, Mongolia, Nigeria, South Africa, Swaziland, Uganda). Finally, we included four countries with 2012 birth estimates >2 million [16] but reported syphilis seroprevalence less than 1% (Brazil, Ethiopia, India, Bangladesh) using the most recently reported GARPR data [14]. This selection process resulted in 30 countries used in the analysis, representing 33% of syphilis-associated adverse pregnancy outcomes globally based upon the most recent (2012) WHO estimates [16].

Estimates of syphilis diagnosed during pregnancy

Number of births by country was obtained from United Nations, Department of Economic and Social Affairs: World Fertility Data (2012) [17]. In order to estimate number of pregnancies by country, number of births by country [17] was adjusted for all-cause stillbirth by adding a stillbirth rate of 18.4 per 1,000 births according to recently published estimates to the number of live births [18]. Estimates of women attending antenatal care (ANC) from selected countries were obtained from the WHO Global Health Observatory [19]. The number of women undergoing syphilis testing during ANC, the syphilis seropositivity estimates, and syphilis test types used were obtained from the 2014 GARPR report [14].

Estimates of current and projected need for benzathine penicillin for treatment of pregnant women with syphilis

Using country-reported ANC syphilis seroprevalence, we calculated the number of pregnant women with a positive syphilis test (treponemal, non-treponemal, non-treponemal with treponemal confirmation, or unknown test type) to estimate the number of benzathine penicillin doses needed to prevent mother-to-child transmission of syphilis. The WHO recommended treatment regimen for early infectious syphilis (primary, secondary, early latent) is one intramuscular injection of 2.4 million units of benzathine penicillin [1]. We assumed that each seroreactive woman would receive at least one injectable dose of 2.4 million units of benzathine penicillin early in pregnancy for treatment of early infectious syphilis and to prevent mother-to-child transmission. Estimates of doses needed for treatment of late stage or unknown stage syphilis were not included due to lack on information on syphilis stage at diagnosis.
Projected needs for benzathine, anticipating that these 30 countries achieve 95% syphilis screening coverage of pregnant women during ANC, were calculated by replacing current screening coverage with 95% for each country reporting a screening coverage less than 95%. For countries with a screening coverage rate at or above 95%, current values were used.

**Estimated need for benzathine penicillin to treat live-born infants of women with syphilis**

WHO treatment guidelines include the recommendation that all infants born to syphilis seropositive mothers receive treatment with a single intramuscular dose of 50,000 IU/kg of benzathine penicillin whether or not the mothers were appropriately treated during pregnancy, regardless of the foetal gestational age at time of treatment [1, 20]. Estimates of penicillin need for live-born infants born to mothers with syphilis assumed 100% treatment coverage of syphilis-seropositive antenatal women and 100% infant survival to treatment.

**Estimates of adverse birth outcomes with and without maternal treatment**

Estimates of the number of women with probable active syphilis, i.e., seroreactivity in screening and confirmatory tests representing infection that could be transmitted from mother to infant during pregnancy, were calculated based upon on a recent meta-analysis [21]. Specifically, a correction factor of 52.2% was applied for countries using non-treponemal testing only, 53.6% for countries using only treponemal testing, and 68.6% for countries not reporting test type [21]. For countries reporting use of both non-treponemal and treponemal testing, 100% of seroreactive women were considered probable active syphilis.

Risk estimates of adverse birth outcomes resulting from untreated probable active maternal syphilis were based on a meta-analysis [3] as follows: any syphilis-associated adverse pregnancy outcomes (52% of untreated syphilis pregnancies), stillbirth (21%) neonatal death (9%), prematurity/low birth weight (14.1%), and other clinical congenital syphilis infections in live born infants (16%).

Estimates of number of adverse birth outcomes averted with treatment of pregnant women with syphilis were calculated using data from a review and meta-analysis evaluating the anticipated reduction in adverse birth outcomes with maternal treatment with benzathine penicillin [4]. Although clinical data and previous studies have identified maternal treatment prior to the third trimester is important in preventing syphilis-associated adverse pregnancy outcomes [22, 23], penicillin treatment is recommended for all seroreactive pregnant women regardless of the foetal gestational age at the time maternal infection was detected. We assumed penicillin was needed for all women identified as having a positive syphilis test result during ANC, regardless of the gestational week of testing. We also assumed 100% treatment of these women estimated as having probable active syphilis during pregnancy. In order to calculate estimates of averted adverse pregnancy outcomes following maternal syphilis treatment, we used previously published estimates by Blencowe et al. We calculated global estimates of pregnancy outcome averted for the following: any adverse pregnancy outcome (84% averted), stillbirth (82% averted), neonatal death (80% averted), prematurity/low birth weight (64% averted) and other clinical congenital syphilis (97% averted) [4].

Projections of the number of adverse pregnancy outcomes averted with increases in ANC syphilis screening coverage to 95% and treatment coverage of 100% were included according to previously described methods.
Results

Estimates of syphilis diagnosed during pregnancy among women attending ANC and estimated current and projected need for benzathine penicillin

Among the 30 countries in this analysis, attendance at one or more ANC visits ranged from 33.9% (Ethiopia) to 98.7% (Mongolia). The percent of women screened for syphilis during ANC ranged from 1.2% (Indonesia) to 100% (Mongolia). Only 7 (28%) countries reported ANC syphilis screening of ≥95%. Syphilis seroprevalence ranged from 0.1% (Honduras) to 11.3% (Liberia). The countries with the highest syphilis seroprevalence were Liberia (11.3%), Mali (9.5%), and Central African Republic (CAR) (7.6%). The country with the largest number of pregnant women seropositive for syphilis was the Democratic Republic of the Congo (1), followed by Tanzania (n = 53,624) and China (n = 30,882). The total number of doses of 2.4 MU of benzathine penicillin needed to treat pregnant women with syphilis in these 30 countries was 351,016 (Table 1), with regional estimates calculated at 244,231 doses for the 17 countries in the Africa Region, 38,724 doses for the 6 countries in the Americas region, and 68,061 doses for the 7 countries in the Asia/Pacific region (Table 1).

Projections of penicillin need if countries were to achieve 95% syphilis screening coverage

Projections of penicillin need if countries were to achieve 95% syphilis screening coverage at current ANC care attendance levels are presented in Table 1. Improving syphilis screening coverage to at least 95% in these 30 countries would increase overall benzathine penicillin need from 351,016 to 712,030 doses (361,014 dose increase) for pregnant women.

With recommended screening rates, countries that would experience the greatest increase in benzathine penicillin need with expanded syphilis screening to 95% include: Indonesia with 74,680 more benzathine penicillin doses needed (from 955 to 75,635 doses), Uganda with 70,891 more doses needed (from 15,672 to 86,563 doses), Nigeria, 44,240 more doses needed (from 8,229 to 52,469 doses) and Mali, 32,665 more doses needed (from 12,769 to 45,434 doses) (Table 1).

Estimated need for paediatric-dosed benzathine penicillin to treat live born infants of women with syphilis

Among these 30 countries, at current syphilis screening coverage, 351,016 doses of paediatric-dosed benzathine penicillin treatment would be needed to treat live born infants of women testing positive for syphilis during pregnancy. The countries with the highest annual number of infants requiring penicillin treatment were DRC (66,985 infants), Tanzania (53,624 infants) and China (30,882 infants) (Table 2).

Projections of benzathine penicillin doses needed for infants if countries were to achieve 95% syphilis screening coverage at current antenatal care attendance levels are presented in Table 2. Improving syphilis screening coverage to at least 95% in these 30 countries would increase overall benzathine penicillin need for infants from 351,016 to 712,030 doses (361,014 dose increase).

Estimates of adverse birth outcomes and those averted with maternal treatment

Test type correction factors along with probable active syphilis infections for each country are displayed in Table 3. The total number of probable active syphilis infections among pregnant
| Country                        | UN Birth (2012) | Birth x0.0184(SB) | Birth +Stillbirth | Number of pregnant women ≥1 ANC visit | Estimated benzathine penicillin doses needed to treat syphilis-positive pregnant women | Additional doses needed with 95% improvement to 95% screening coverage | Doses needed with 95% syphilis screening coverage | Antenatal syphilis prevalence (%) | Number of pregnant women tested for syphilis | Percent pregnant women attending ≥1 ANC visit | Number of pregnant women attending ≥1 ANC visit |
|-------------------------------|-----------------|-------------------|-------------------|---------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Africa                        |                 |                   |                   |                                       |                                                                                  |                                                                                |                                                                                  |                                  |                                  |                                  |                                  |
| Burkina Faso                 | 658,561         | 12,118            | 660,679           | 94.9                                  | 636,474                                                                          | 2,903                                                                          | 7,638                                                                          | 0.91                             | 100                              | 100                              | 636,474                          |
| Central African Republic      | 116,036         | 2,135             | 118,171           | 56.6                                  | 64,501                                                                          | 35.8                                                                          | 23,099                                                                        | 1.2                 | 100                              | 100                              | 64,501                           |
| Chad                         | 4,232,264       | 7512              | 4,278,776         | 82.1                                  | 2,300,324                                                                       | 177,121                                                                      | 2,300,324                                                                       | 1.2                 | 100                              | 100                              | 2,300,324                        |
| Democratic Republic of Congo | 2,800,977       | 51,538            | 2,852,515         | 96.4                                  | 1,272,728                                                                       | 201                             | 2,300,324                                                                       | 1.2                 | 100                              | 100                              | 2,300,324                        |
| Ethiopia                      | 683,954         | 12,972            | 706,926           | 94.4                                  | 685,544                                                                         | 14                               | 230,954                                                                       | 1.2                 | 100                              | 100                              | 230,954                          |
| Ghana                        | 1,304,457       | 24,003            | 1,328,460         | 91.5                                  | 1,159,568                                                                       | 14                               | 1,328,460                                                                       | 1.2                 | 100                              | 100                              | 1,328,460                        |
| Kenya                         | 1,304,457       | 24,003            | 1,328,460         | 91.5                                  | 1,159,568                                                                       | 14                               | 1,328,460                                                                       | 1.2                 | 100                              | 100                              | 1,328,460                        |
| Lesotho                      | 1,304,457       | 24,003            | 1,328,460         | 91.5                                  | 1,159,568                                                                       | 14                               | 1,328,460                                                                       | 1.2                 | 100                              | 100                              | 1,328,460                        |
| Malawi                       | 622,846         | 12,012            | 634,858           | 82.1                                  | 545,849                                                                         | 27                               | 323,814                                                                       | 1.2                 | 100                              | 100                              | 323,814                          |
| Marshall Islands              | 597,056         | 17,044            | 614,094           | 90.6                                  | 267,810                                                                         | 36                               | 323,814                                                                       | 1.2                 | 100                              | 100                              | 323,814                          |
| Mozambique                   | 2,800,977       | 51,538            | 2,852,515         | 96.4                                  | 1,272,728                                                                       | 201                             | 2,300,324                                                                       | 1.2                 | 100                              | 100                              | 2,300,324                        |
| Saudi Arabia                  | 2,532,264       | 46,933            | 2,579,196         | 86.2                                  | 2,300,324                                                                       | 177,121                                                                      | 2,300,324                                                                       | 1.2                 | 100                              | 100                              | 2,300,324                        |
| South Africa                  | 1,856,881       | 34,363            | 1,891,244         | 96.8                                  | 1,439,946                                                                       | 98                               | 1,439,946                                                                       | 1.2                 | 100                              | 100                              | 1,439,946                        |
| Swaziland                    | 1,856,881       | 34,363            | 1,891,244         | 96.8                                  | 1,439,946                                                                       | 98                               | 1,439,946                                                                       | 1.2                 | 100                              | 100                              | 1,439,946                        |
| Tanzania                     | 1,610,398       | 26,631            | 1,637,029         | 72.2                                  | 1,439,946                                                                       | 98                               | 1,439,946                                                                       | 1.2                 | 100                              | 100                              | 1,439,946                        |
| Uganda                       | 1,407,179       | 25,862            | 1,433,041         | 94.9                                  | 1,350,984                                                                       | 72                               | 1,350,984                                                                       | 1.2                 | 100                              | 100                              | 1,350,984                        |
| Zambia                       | 512,365         | 9,426             | 521,731           | 95.7                                  | 390,284                                                                         | 50                               | 390,284                                                                       | 1.2                 | 100                              | 100                              | 390,284                          |
| Total                        |                 |                   |                   |                                       |                                                                                  |                                                                                |                                                                                  |                                  |                                  |                                  |                                  |
| Africa                        |                 |                   |                   |                                       |                                                                                  |                                                                                |                                                                                  |                                  |                                  |                                  |                                  |
| Americas                     |                 |                   |                   |                                       |                                                                                  |                                                                                |                                                                                  |                                  |                                  |                                  |                                  |
| Argentina                    | 756,176         | 13,914            | 770,090           | 98.1                                  | 755,458                                                                         | 1.2                             | 755,458                                                                         | 0.91                             | 100                              | 100                              | 755,458                          |
| Brazil                       | 2,341,309       | 41,967            | 2,383,276         | 85.8                                  | 2,744,875                                                                       | 1.0                             | 7,434                                                                         | 1.2                 | 100                              | 100                              | 7,434                            |
| Haiti                        | 261,639         | 4,314             | 265,953           | 94.5                                  | 225,153                                                                         | 0.8                             | 225,153                                                                         | 1.2                 | 100                              | 100                              | 225,153                          |
| Uganda                       | 180,000         | 3,133             | 183,133           | 94.2                                  | 172,720                                                                         | 0.1                             | 172,720                                                                         | 1.2                 | 100                              | 100                              | 172,720                          |
| Total                        |                 |                   |                   |                                       |                                                                                  |                                                                                |                                                                                  |                                  |                                  |                                  |                                  |
| Total                        | 21,542,717      | 396,386           | 21,939,103        | 75.7                                  | 16,194,966                                                                      | 9.6                             | 16,194,966                                                                      | 1.2                 | 100                              | 100                              | 16,194,966                       |

Table 1. Estimated annual needs of benzathine penicillin for pregnant women with syphilis in 30 high-morbidity countries.
Table 1. (Continued)

| Country          | UN Birth (2012) | Number of stillbirths | Number of pregnancies | Percent pregnant women attending ≥ 1 ANC visit | Number of pregnant women attending ≥ 1 ANC visit | Percent pregnant women tested for syphilis | Number of pregnant women tested for syphilis | Antenatal syphilis prevalence (%) | Number of pregnant women testing positive for syphilis | Estimated benzathine penicillin doses needed to treat syphilis-positive pregnant women | Doses needed with improvement to 95% screening coverage | Additional doses needed with 95% syphilis screening coverage |
|------------------|------------------|------------------------|-----------------------|-----------------------------------------------|-----------------------------------------------|------------------------------------------|---------------------------------------|---------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------|
| Bangladesh       | 3,669,345        | 67,516                 | 3,736,861             | 58.7                                          | 2,193,537                                    | 58.3                                     | 1,278,832                            | 0.5                             | 6,394                                            | 6,394                                                                                | 10,419                                          | 4,025                                            |
| China*           | 16,040,000       | 295,136                | 16,335,136            | 95.0                                          | 15,518,379                                   | 99.5                                     | 15,440,787                          | 0.2                             | 30,882                                           | 30,882                                                                               | 30,882                                          | 0                                                |
| India            | 27,063,977       | 497,977                | 27,561,954            | 75.1                                          | 20,699,028                                   | 65.1                                     | 13,475,067                          | 0.2                             | 26,950                                           | 26,950                                                                               | 39,328                                          | 12,378                                          |
| Indonesia*       | 4,805,298        | 88,417                 | 4,893,715             | 95.7                                          | 4,683,286                                    | 1.2                                      | 56,199                               | 1.7                             | 955                                              | 955                                                                                   | 75,635                                          | 74,680                                          |
| Mongolia         | 63,270           | 1,164                  | 64,434                | 98.7                                          | 63,597                                       | 97.2                                     | 61,816                               | 2.6                             | 1,607                                            | 1,607                                                                                | 1,607                                           | 0                                                |
| Myanmar*         | 811,644          | 14,934                 | 826,578               | 83.1                                          | 668,887                                      | 10                                      | 68,689                               | 0.7                             | 481                                              | 481                                                                                   | 4,568                                           | 4,087                                           |
| Papua New Guinea*| 197,492          | 3,634                  | 201,126               | 66.0                                          | 132,743                                      | 8.9                                      | 11,814                               | 6.7                             | 792                                              | 792                                                                                   | 8,449                                           | 7,658                                           |
| Regional Totals  | 52,651,026       | 968,779                | 53,619,805            | 43,977,456                                    | 30,393,205                                   | 68,061                                   | 68,061                               | 170,888                          | 102,827                                          |                                                                                       |                                                 |                                                   |
| 30-Country Totals| 78,823,428       | 1,450,351              | 80,273,779            | 64,657,035                                    | 42,101,982                                   | 351,016                                  | 351,016                              | 712,030                          | 361,014                                          |                                                                                       |                                                 |                                                   |

*WHO investment case country

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Table 2. Estimated paediatric benzathine penicillin regimens needed for treatment of infants exposed to syphilis during pregnancy in 30 high-morbidity countries.

| Country                          | Number of pregnant women testing positive for syphilis | Estimated paediatric benzathine penicillin doses needed assuming 100% maternal treatment and 100% infant survival | Number of pregnant women testing positive for syphilis assuming 95% maternal screening coverage | Estimated paediatric benzathine penicillin doses needed with 95% maternal screening coverage, 100% maternal treatment, and 100% infant survival | Additional paediatric doses needed with 95% maternal syphilis screening coverage |
|----------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                                  | A (Table 1) | B | D | E | F |
| Africa                           |             |   |   |   |   |
| Burkina Faso                     | 7,638       | 7,638 | 7,638 | 7,638 | 0 |
| Central African Republic         | 1,755       | 1,755 | 4,658 | 4,658 | 2,903 |
| Chad                             | 6,022       | 6,022 | 6,022 | 6,022 | 0 |
| Democratic Republic of Congo     | 66,985      | 66,985 | 87,412 | 87,412 | 20,427 |
| Ethiopia                         | 2,446       | 2,446 | 8,268 | 8,268 | 5,822 |
| Ghana                            | 3,492       | 3,492 | 9,786 | 9,786 | 6,294 |
| Kenya                            | 11,964      | 11,964 | 16,167 | 16,167 | 4,203 |
| Liberia                          | 1,717       | 1,717 | 14,692 | 14,692 | 12,975 |
| Madagascar                       | 9,758       | 9,758 | 30,595 | 30,595 | 20,837 |
| Mali                             | 12,769      | 12,769 | 45,434 | 45,434 | 32,665 |
| Mozambique                       | 17,043      | 17,043 | 34,970 | 34,970 | 17,927 |
| Nigeria                          | 8,229       | 8,229 | 52,469 | 52,469 | 44,240 |
| South Africa                     | 12,493      | 12,493 | 15,931 | 15,931 | 3,438 |
| Swaziland                        | 1,093       | 1,093 | 1,093 | 1,093 | 0 |
| Tanzania                         | 53,624      | 53,624 | 53,624 | 53,624 | 0 |
| Uganda                           | 15,672      | 15,672 | 86,563 | 86,563 | 70,891 |
| Zambia                           | 11,530      | 11,530 | 21,819 | 21,819 | 10,290 |
| **Regional Totals**              | **244,231** | **244,231** | **497,142** | **497,142** | **252,911** |
| Americas                         |             |   |   |   |   |
| Argentina                        | 7,842       | 7,842 | 8,612 | 8,612 | 771 |
| Bolivia                          | 2,006       | 2,006 | 2,758 | 2,758 | 752 |
| Brazil                           | 21,989      | 21,989 | 23,341 | 23,341 | 1,351 |
| Haiti                            | 6,006       | 6,006 | 8,342 | 8,342 | 2,336 |
| Honduras                         | 98          | 98   | 164   | 164   | 66  |
| Uruguay                          | 783         | 783  | 783   | 783   | 0   |
| **Regional Totals**              | **38,724** | **38,724** | **44,000** | **44,000** | **5,276** |
| Asia/Pacific                     |             |   |   |   |   |
| Bangladesh                       | 6,394       | 6,394 | 10,419 | 10,419 | 4,025 |
| China                            | 30,882      | 30,882 | 30,882 | 30,882 | 0   |
| India                            | 26,950      | 26,950 | 39,328 | 39,328 | 12,378 |

(Continued)
women in these 30 countries was 219,638. Assuming no maternal treatment was available, overall estimated adverse birth outcomes due to congenital syphilis among these probable active syphilis cases were 114,212 overall, (46,124 stillbirths, 19,767 neonatal deaths, 13,178 premature delivery/low birth weight, and 35,142 clinical congenital syphilis infections) (Table 3).

Assuming availability of penicillin and treatment for all mothers diagnosed with syphilis and using current syphilis screening coverage, an estimated 95,938 adverse birth outcomes overall would be prevented. This would include 37,822 stillbirths, 15,814 neonatal deaths, 8,434 prematurity/low birth weight, and 34,088 congenital syphilis cases (Table 3).

Projections of overall adverse birth outcomes averted if these countries were to achieve 95% syphilis screening and 100% treatment coverage of women with probable active syphilis are presented in Table 3. At current ANC attendance levels and ANC seroprevalence, 394,035 adverse pregnancy outcomes could be averted with screening improvements to 95% of ANC attendees and 100% treatment coverage (Table 3).

**Discussion**

In response to reports of benzathine penicillin shortage, we analysed ANC syphilis surveillance data from 30 high-morbidity countries representing only one-third of estimated syphilis-associated adverse birth outcomes to inform efforts to ensure stable supplies of benzathine penicillin. Using current ANC attendance and syphilis screening coverage, we estimated an immediate need for approximately 350,000 doses of benzathine penicillin to treat pregnant women seropositive for syphilis and an additional 350,000 doses of paediatric-dosed benzathine penicillin to treat infants exposed to syphilis during pregnancy. Current need is greatest in Africa, followed by Asia and the Americas regions. Assuming each of the pregnant women in this analysis were treated with at least 2.4 million units benzathine penicillin as recommended by WHO, more

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**Table 2. (Continued)**

| Country          | Number of pregnant women testing positive for syphilis | Estimated paediatric benzathine penicillin doses needed assuming 100% maternal treatment and 100% infant survival | Number of pregnant women testing positive for syphilis assuming 95% maternal screening coverage | Estimated paediatric benzathine penicillin doses needed with 95% maternal screening coverage, 100% maternal treatment, and 100% infant survival | Additional paediatric doses needed with 95% maternal syphilis screening coverage |
|------------------|-------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
|                  | A                                               | B                                      | D                                      | E                                      | F                                      |
|                  | Table 1                                         | A                                      | Table 1                                | D                                      | E                                      |
| Indonesia        | 955                                             | 955                                    | 75,635                                 | 75,635                                 | 74,680                                 |
| Mongolia         | 1,607                                           | 1,607                                  | 1,607                                  | 1,607                                  | 0                                      |
| Myanmar          | 481                                             | 481                                    | 4,568                                  | 4,568                                  | 4,087                                  |
| Papua New Guinea | 792                                             | 792                                    | 8,449                                  | 8,449                                  | 7,658                                  |
| **Regional Totals** | **68,061**                                     | **68,061**                             | **170,888**                            | **170,888**                            | **102,827**                            |
| **30-Country Totals** | **351,016**                                    | **351,016**                           | **712,030**                            | **712,030**                            | **361,014**                            |

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Table 3. Estimates of syphilis-associated adverse birth outcomes and estimates of those averted through maternal treatment with benzathine penicillin in 30 high-morbidity countries.

| Region/Country                  | Number of pregnant women with probable active syphilis | Current ANC Syphilis Screening Coverage | 95% Screening Coverage |
|---------------------------------|--------------------------------------------------------|----------------------------------------|-------------------------|
|                                 | Number of women testing positive for syphilis | Syphilis diagnostic test type correction factor (%) | Number of pregnant women testing positive for syphilis | Stillbirths expected without treatment (84%) | Stillbirths averted with treatment (82%) | Neonatal deaths expected without treatment (8%) | Neonatal deaths averted with treatment (80%) | Premature/low birth weight births expected without treatment (6%) | Premature/low birth weight births averted with treatment (64%) | Clinical infections in live born infants expected without treatment (16%) | Clinical infections in live born infants averted with treatment (97%) | Number of pregnant women with probable active syphilis | Number of adverse pregnancy outcomes averted all women treated (84%) |
|                                 | Number of pregnant women with probable active syphilis | Any adverse birth outcomes expected without treatment (52%) | Neonatal deaths expected without treatment (21%) | Stillbirths expected without treatment (84%) | Stillbirths averted with treatment (82%) | Neonatal deaths expected without treatment (8%) | Neonatal deaths averted with treatment (80%) | Premature/low birth weight births expected without treatment (6%) | Premature/low birth weight births averted with treatment (64%) | Clinical infections in live born infants expected without treatment (16%) | Clinical infections in live born infants averted with treatment (97%) | Number of pregnant women with probable active syphilis | Number of adverse pregnancy outcomes averted all women treated (84%) |
|                                 | Number of pregnant women with probable active syphilis | Any adverse birth outcomes expected without treatment (52%) | Neonatal deaths expected without treatment (21%) | Stillbirths expected without treatment (84%) | Stillbirths averted with treatment (82%) | Neonatal deaths expected without treatment (8%) | Neonatal deaths averted with treatment (80%) | Premature/low birth weight births expected without treatment (6%) | Premature/low birth weight births averted with treatment (64%) | Clinical infections in live born infants expected without treatment (16%) | Clinical infections in live born infants averted with treatment (97%) | Number of pregnant women with probable active syphilis | Number of adverse pregnancy outcomes averted all women treated (84%) |
|                                 | Number of pregnant women with probable active syphilis | Any adverse birth outcomes expected without treatment (52%) | Neonatal deaths expected without treatment (21%) | Stillbirths expected without treatment (84%) | Stillbirths averted with treatment (82%) | Neonatal deaths expected without treatment (8%) | Neonatal deaths averted with treatment (80%) | Premature/low birth weight births expected without treatment (6%) | Premature/low birth weight births averted with treatment (64%) | Clinical infections in live born infants expected without treatment (16%) | Clinical infections in live born infants averted with treatment (97%) | Number of pregnant women with probable active syphilis | Number of adverse pregnancy outcomes averted all women treated (84%) |
|                                 | Number of pregnant women with probable active syphilis | Any adverse birth outcomes expected without treatment (52%) | Neonatal deaths expected without treatment (21%) | Stillbirths expected without treatment (84%) | Stillbirths averted with treatment (82%) | Neonatal deaths expected without treatment (8%) | Neonatal deaths averted with treatment (80%) | Premature/low birth weight births expected without treatment (6%) | Premature/low birth weight births averted with treatment (64%) | Clinical infections in live born infants expected without treatment (16%) | Clinical infections in live born infants averted with treatment (97%) | Number of pregnant women with probable active syphilis | Number of adverse pregnancy outcomes averted all women treated (84%) |
|                                 | Number of pregnant women with probable active syphilis | Any adverse birth outcomes expected without treatment (52%) | Neonatal deaths expected without treatment (21%) | Stillbirths expected without treatment (84%) | Stillbirths averted with treatment (82%) | Neonatal deaths expected without treatment (8%) | Neonatal deaths averted with treatment (80%) | Premature/low birth weight births expected without treatment (6%) | Premature/low birth weight births averted with treatment (64%) | Clinical infections in live born infants expected without treatment (16%) | Clinical infections in live born infants averted with treatment (97%) | Number of pregnant women with probable active syphilis | Number of adverse pregnancy outcomes averted all women treated (84%) |

(Continued)
### Table 3. Current ANC Syphilis Screening Coverage

| Region/Country | Number of pregnant women with probable active syphilis | Syphilis diagnostic test type correction factor (%) | Number of women testing positive for syphilis | Any adverse birth outcomes expected without treatment (92%) | Adverse birth outcomes averted with treatment (84%) | Stillbirths expected without treatment (21%) | Stillbirths averted with treatment (82%) | Neonatal deaths expected without treatment (9%) | Neonatal deaths averted with treatment (80%) | Premature/low birth weight births expected without treatment (64%) | Premature/low birth weight births averted with treatment (64%) | Clinical infections in live born infants expected without treatment (16%) | Clinical infections in live born infants averted with treatment (97%) | Number of pregnant women with probable active syphilis | Number of adverse pregnancy outcomes averted all women treated (84%) |
|----------------|-------------------------------------------------------|--------------------------------------------------|---------------------------------------------|-----------------------------------------------------------|-------------------------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| India          | 26,950                                                | 52.2                                            | 14,068                                      | 7,315                                                      | 6,145                                           | 2,954                                       | 2,423                                       | 1,266                                           | 1,013                                           | 844                                         | 540                                         | 2,251                                         | 2,183                                         | 20,529                                         | 17,245                                         |
| Indonesia      | 955                                                   | 100                                             | 955                                         | 497                                                        | 417                                             | 201                                         | 165                                         | 86                                              | 69                                              | 57                                           | 37                                          | 153                                          | 148                                          | 75,635                                         | 63,533                                         |
| Mongolia       | 1,607                                                 | 68.6                                            | 1,103                                       | 573                                                        | 482                                             | 232                                         | 190                                         | 99                                              | 79                                              | 66                                           | 42                                          | 176                                          | 171                                          | 1,103                                          | 926                                            |
| Myanmar        | 481                                                   | 68.6                                            | 330                                         | 172                                                        | 144                                             | 69                                          | 57                                          | 30                                              | 24                                              | 20                                           | 13                                          | 53                                           | 51                                           | 3,134                                          | 2,623                                          |
| Papua New Guinea | 792                                                 | 53.6                                            | 546                                         | 284                                                        | 239                                             | 115                                         | 94                                          | 49                                              | 39                                              | 33                                           | 21                                          | 87                                           | 85                                           | 5,796                                          | 4,869                                          |
| Regional Totals | 68,061                                               | 51.31                                           | 26,682                                      | 8,269                                                      | 6,227                                           | 2,243                                       | 1,813                                       | 973                                             | 803                                             | 579                                          | 47                                          | 210                                          | 206                                          | 142,663                                        | 119,837                                        |
| 30-Country Totals | 351,016                                             | 219.63                                          | 114,212                                     | 37,822                                                     | 19,767                                          | 15,814                                     | 11,178                                     | 8,434                                           | 5,314                                           | 3,304                                         | 2,450                                       | 1,589                                         | 1,204                                         | 469,089                                        | 394,035                                        |

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than 95,000 adverse pregnancy outcomes due to maternal syphilis would be averted in these
countries.

The WHO initiative to eliminate congenital syphilis calls for at least 95% of pregnant
women to receive ANC, at least 95% of these pregnant women to be tested for syphilis during
prenatal care and at least 95% of syphilis-infected (seroreactive) pregnant women to receive
treatment [12]. Although ANC attendance was 95% or greater for approximately half of these
30 countries, less than one-third of countries performed syphilis screening for ≥95% of ANC
populations. As countries work to achieve the elimination targets, benzathine penicillin need
will increase. Our projections suggest an approximate doubling of annual penicillin need for
pregnant women and infants if these 30 countries were to strive for and achieve at least 95%
coverage for syphilis screening, a value that would be higher with improvements in ANC cover-
age and greatest in Africa.

WHO recommends that all infants born to seropositive mothers receive treatment with a
single intramuscular dose of benzathine penicillin regardless of whether the mother received
treatment during pregnancy [1]. These paediatric penicillin estimates demonstrate need for
penicillin formulations, including benzathine that can be reliably weight-adjusted to assure
proper dosing. Current pre-filled syringes offer the dosing options of 600 thousand or 1.2 or
2.4 million units of benzathine penicillin, amounts not easily weight-adjustable for newborn
infant treatment [24–25]. Efforts to engage manufacturers regarding the supply and dosing
needs of these high-morbidity countries are needed to promote production of benzathine peni-
cillin that can be correctly weight-dosed for infants at affordable cost.

A single dose of benzathine penicillin treatment ends infectivity in adults, and if received
sufficiently early in pregnancy will treat the mother and prevent or treat congenital syphilis in
the foetus. Penicillin treatment is safe and allergy is a very rare event (4 cases/million). [26]
Our adverse birth outcome estimates among women with syphilis necessarily assumes that
these women either received no treatment or were treated too late in pregnancy to prevent
mother-to-child transmission of syphilis. Published studies suggest that early detection and
treatment of syphilis in pregnancy is critical as delayed treatment, after the first trimester, can
still result in syphilis-associated adverse outcomes [22, 23]. This was corroborated by a recent
analysis indicating that among syphilitic women treated in the third trimester, 64.4% of preg-
nancies had poor pregnancy outcomes compared with 13.3% of pregnancies in syphilitic
women treated in the first trimester, and 13.7% of pregnancies in women without syphilis.
[27]. In this analysis, projected adverse pregnancy outcomes averted with maternal penicillin
treatment were high, particularly among African countries. These estimates of country-level
maternal syphilis burden and preventable adverse pregnancy outcomes with treatment of syph-
ilis-infected pregnant women can be used in planning and projecting need for dependable
national supplies of benzathine penicillin.

There are limitations in deriving penicillin need from these estimates. Low testing coverage
of pregnant women in some countries with high ANC syphilis prevalence underestimates
benzathine penicillin need were testing coverage to improve. Also, infants with symptomatic
congenital syphilis should receive additional treatment with aqueous crystalline penicillin
according to WHO treatment guidelines [1]. We did not generate estimates of need for this for-
mulation of penicillin (aqueous) for infants. We estimated paediatric benzathine penicillin
need on the assumptions of 100% treatment of mothers with positive syphilis test results and
100% survival of infants; syphilis-associated stillbirth and neonatal death resulting from no or
late maternal treatment would reduce the number of paediatric doses needed [25]. We did not
account for treatment needs of pregnant women with late latent stage syphilis which requires
more than one dose of benzathine penicillin. We did not address timing of treatment during
pregnancy, thus, the number of CS cases averted could be fewer in situations where maternal
treatment occurred late in pregnancy, even if the infants could be successfully treated after birth. Penicillin needs estimates for pregnant women and infants were based on maternal syphilis seroprevalence which does not accurately reflect active syphilis infection due to variations in syphilis test type by country. We did not include a sensitivity analysis or any measure of variability. Studies have identified other barriers to treatment not related to penicillin supply [22]. We did not address these. We did not address drug shipment, storage, or supply challenges such as product loss due to expiration or other inventory management issues. Recent syphilis incidence estimates for adults ages 15–49 indicate 5.6 million new syphilis cases occur globally each year [28]. This analysis focused only on syphilis in pregnancy and does not evaluate countries’ needs for benznathine penicillin for treatment of sex partners of syphilis-infected women to prevent reinfection, non-pregnant adults with sexually-acquired syphilis, or for other conditions such as rheumatic heart disease or other streptococcal infections [29].

Of all syphilis-infected persons, pregnant women and their infants are the most vulnerable. Recently reported data indicate that progress has been made since the 2007 launch of the elimination of congenital syphilis initiative; however, the global maternal syphilis burden remains high with more than 900,000 estimated maternal syphilis infections resulting in 350,000 adverse birth outcomes in 2012 [15]. The maternal morbidity due to syphilis in these 30 countries accounts for one-fifth of the estimated global maternal burden and approximately one-third of estimated adverse pregnancy outcomes due to congenital syphilis. Needs estimates of benznathine penicillin can help ensure needed treatment is available for pregnant women and their infants and anticipate increased demand. With development, validation, and expanded use of rapid syphilis tests, including dual rapid HIV/syphilis tests [30], syphilis screening during ANC is expected to increase as is same-day penicillin treatment of pregnant women testing positive for syphilis.

Ensuring a continuous global supply of benznathine penicillin to match increasing global demand is a critical component of preventing infant morbidity and mortality associated with syphilis in pregnancy. These needs estimates provide scope and scale in addressing high-morbidity country needs for benznathine penicillin. Assessing benznathine penicillin need is but one component of a broader evaluation of congenital syphilis prevention through maternal syphilis screening during ANC. WHO, in collaboration with international partners, has spearheaded an initiative to assess global supply, current and projected demand, and production capacity for benznathine penicillin. Further evaluation is needed to identify and address other barriers to treatment of pregnant women with syphilis at local, country, and regional levels.

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Author Contributions
Conceived and designed the experiments: MT SNF XZ LH MK JK. Analyzed the data: MT SNF MK. Wrote the paper: MT SNF MK NB JK.

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