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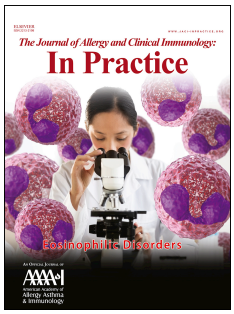

Oral Challenge with Trimethoprim-Sulfamethoxazole in Patients with "Sulfa" Antibiotic Allergy

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Clinical Implications: For patients with a non-severe immediate or delayed history of an unspecified sulfa or TMP-SMX allergy and an upcoming need for treatment or prophylaxis, direct oral challenge with TMP-SMX is a safe and efficacious procedure.

To the Editor: "Sulfa" antibiotic allergy is the second most commonly reported class of outpatient antibiotic allergy.[1] The "sulfa" allergy label subsequently limits use of trimethoprim-sulfamethoxazole, (TMP-SMX), which is a preferred agent for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.[2] Non-antibiotic sulfa containing drugs are not cross-reactive with sulfonamide antibiotics and importantly differ from sulfonamide antibiotics by the absence of an arylamine group linked to the benzene ring at N4 and an aromatic 5 or 6 member ring attached to the sulfonamide core as an N1 substituent.[3,4]

Although most reported reactions to sulfonamide antibiotics are non-IgE-mediated, severe T-cell mediated reactions such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug induced nephritis or hepatitis do occur and are strict contraindications to future TMP-SMX use.[5] Current guidelines to manage TMP-SMX treatment in patients with mild to moderate skin rash without systemic features include desensitization protocols.[4] However, desensitization is a lengthy procedure that does not prove or disprove the

allergy. So, if patients require TMP-SMX subsequently, they would need to be desensitized again.[6] The safest and most efficacious approach to rechallenge with sulfonamide antibiotics in non-HIV infected labeled patients is largely unknown; however, common practice includes multiple dose rechallenge over several hours. We examined the safety and outcomes of single or two dose TMP-SMX oral challenges in adults whose history was inconsistent with a severe delayed immune mediated reaction, and their subsequent tolerance of future TMP-SMX treatment.

Our study presents a retrospective cohort study done under institutional review board (IRB) approved protocols from Vanderbilt University Medical Center (VUMC), IRB #161455. Between October 2015 and February 2019, 204 sequential patients with history-based past immediate, non-severe delayed, or unknown reactions to TMP-SMX or unspecified "sulfa" antibiotics with ongoing avoidance of TMP-SMX underwent direct observed oral challenges with TMP-SMX in a dedicated outpatient drug allergy clinic at VUMC. Patients with any history of a severe delayed immune mediated reaction, such as SJS, TEN, DRESS, AGEP, or drug induced nephritis or hepatitis, were excluded (**Table E1**, available in this article's Online Repository at www.jaci-inpractice.org). Patients were selected to receive a two dose TMP-SMX (8-40mg;80-400mg) challenge with a one-hour observation interval in between if they met the following criteria: 1) History of multiple cutaneous, respiratory or cardiovascular symptoms compatible with anaphylaxis or an IgE-mediated reaction at any time in the past (e.g. urticaria, angioedema, shortness of breath or hypotension); 2) History of non-severe immediate (<1 hour) or accelerated (> 1 hour to <36 hours) within the past 5 years (e.g. isolated urticaria, maculopapular rash or gastrointestinal symptoms); 3) Significant patient anxiety surrounding

single dose challenge. A single dose TMP-SMX (80-400mg) challenge was administered if there was a history of non-severe delayed reactions without multiple features consistent with IgE mediated reaction, non-severe immediate reaction (< 1 hour) greater than 5 years ago, non-severe accelerated reaction (> 1 hour to < 36 hours) greater than 5 years ago, or unknown, remote history (**Table E1**, available in this article's Online Repository at www.jaci-inpractice.org). Patients were monitored for 2 hours after each full strength challenge dose in clinic for any immediate reaction and were contacted by phone 24-hours after challenge to follow-up any delayed reaction. Oral challenge success was defined by the absence of any symptoms during the observed challenge and 24-hour follow up period. Oral challenge success resulted in the removal of the "sulfa" or TMP-SMX allergy label from the chart and patient education that TMP-SMX could now be used in their clinical care.

Charts were reviewed for patient demographics (age, sex and race), time between index reaction and challenge, index reaction history (immediate, delayed, unknown), indication for consult (multi-drug allergy, anticipated need for treatment, need for prophylaxis, or infection without other options), co-morbidities (HIV, diabetes, MRSA, and transplant), nature of initial label (TMP-SMX or unspecified sulfa), and type of challenge performed (single or two dose). Follow-up assessment to determine tolerance of any subsequent TMP-SMX treatments was performed by chart review, email survey and telephone survey. In follow up, patients were asked if they had taken TMP-SMX for treatment and if an adverse drug reaction was experienced.

The relationship between age, sex, race, HIV status, reported reaction history and time since original reaction with the outcome of oral challenge failure were assessed using Fisher's exact

test, Wilcoxon rank-sum tests, and univariate logistic regression. These covariates were selected *a priori* for their potential as predictors of challenge failure based upon clinical experience during the performance of the challenges. A multivariable logistic regression was performed to adjust for confounding amongst these covariates and utilized 10 degrees of freedom in a total sample size of 204 patients.

The demographic and clinical characteristics of the 204 patients are described in **Table 1**. Of 204 patients, 195 (95.6%) were HIV non-infected and 9 (4.4%) were HIV infected (**Figure 1**). Oral challenge was tolerated by 191/204 (94%) patients; with 171/179 (96%) of single dose and 20/25 (80%) of two dose challenges tolerated. Of patients with a TMP-SMX allergy or unspecified "sulfa" allergy, 89% (97/109) and 98.9% (94/95) tolerated a single or two dose challenge, respectively. Of the 13 patients who met the definition for oral challenge failure, reactions were non-severe (**Table E2**, available in this article's Online Repository at www.jaci-inpractice.org).

By index history, 3/23 (13%) of patients with an immediate hypersensitivity history failed oral challenge, compared to 9/106 (8.5%) with a non-severe delayed history or an unknown history 1/75 (1%), Fisher's exact test p-value=0.03. A "non-immediate" index reaction history (defined by either a non-severe delayed or unknown history of original sulfa reaction), showed a reduced risk of challenge failure compared to a history consistent with an immediate reaction, with an unadjusted odds ratio (OR) 0.36 (95% CI 0.15, 0.86), p =0.02. By nature of initial label, 12/109 (11%) of patients with a TMP-SMX allergy label failed oral challenge compared to 1/95 (1%) with an unspecified sulfa allergy label, p-value=0.003. In patients that underwent a single dose

challenge, 8/179 (5%) failed compared to 5/25 (20%) of two dose challenge patients, p-value=0.01. Of the 25 patients that underwent a two dose challenge, 8/25 (32%) patients had an immediate index reaction history, including 2 of reported anaphylaxis, 16/25 (64%) had a delayed index reaction history, and 1/25 (4%) had an unknown history (**Table E3**, available in this article's Online Repository at www.jaci-inpractice.org). 37 patients did not know the amount of time elapsed since their original reaction, but in patients who could provide this information, significantly more time had elapsed since original reaction in patients who passed oral challenge (median 20 years, interquartile range [10, 40]), versus failed (median 3 years, interquartile range [1, 10]), Wilcoxon-rank sum p-value <0.005. In univariate logistic regression, a one-year increase in time since reported reaction was associated with a decreased risk of oral challenge failure, with an unadjusted OR 0.87 (95% CI 0.80, 0.96), p =0.005.

In our a priori multivariable adjusted logistic regression model including age, sex, race, HIV status, time since index reaction, and reaction history, time since reaction was significantly associated with reduced risk of challenge failure, adjusted OR 0.88 per year (95% CI 0.80, 0.97, p-value =0.01 (**Figure E1**, available in this article's Online Repository at www.jaci-inpractice.org). A "non-immediate" history was also associated with reduction in the risk of challenge failure 0.26 (95% CI 0.06, 1.10) p =0.05.

Of the 52/191 (27%) challenge negative patients who reported subsequent TMP-SMX treatment during follow-up surveys, 43/52 (83%) patients tolerated all of their subsequent TMP-SMX courses, with a total of 63/72 of all TMP-SMX courses tolerated. There were 9 reported adverse

events leading to treatment cessation, all of which were mild (**Table E4**, available in this article's Online Repository at www.jaci-inpractice.org).

A limitation of our study is that it is retrospective, making it potentially difficult to capture the true number of patients who have received TMP-SMX treatment post-challenge. We addressed this by using phone and email surveys. It is also possible that some patients labeled with "sulfa" antibiotic allergy or oral challenge failures were not a result of hypersensitivity reactions to sulfamethoxazole but rather trimethoprim alone.[7] In addition, 2 patients reported as having diagnosed anaphylaxis passed two dose oral challenge, and overall 5 patients who had immediate histories potentially compatible with anaphylaxis as characterized by immediate reactions with multisystem involvement were challenged. It is notable that all 4 of the 5 patients who passed oral challenge had reactions of remote or unknown latency, and the one patient who failed had an index reaction less than 1 year from challenge (**Table E3**, available in this article's Online Repository at www.jaci-inpractice.org). The generalizability of this approach warrants further study; however, at present, it seems prudent that desensitization be the approach for patients with a history compatible with anaphylaxis. Although our numbers are small, our data also suggests that patients with a remote history of anaphylaxis (i.e. > 5 years) will be much less likely to react than those with more recent reactions. Further, our study supports the use of oral challenge in patients with a non-severe immediate reaction history; however, the safety of this approach is limited by the low sample size of patients with an immediate reaction history, 23/204 (11%). HIV status has been described as an independent risk factor for sulfonamide antibiotic allergy, for which desensitization approaches have been shown to be effective.[8-9] A previous study also suggested that 70% or more of HIV patients with sulfonamide antibiotic allergies rechallenged to

TMP-SMX will be tolerant.[9] Our study supported an oral challenge failure rate in HIV infected patients of 2/9 (22.2%) (**Table 1**) which is similar to the rate observed by larger HIV specific cohorts.[9] A major aim of our study was to demonstrate the safety and efficacy of single dose oral challenge with TMP-SMX in non-HIV infected patients and subsequent tolerance of sulfonamide antibiotics, which we accomplished.

This is the first study that reports on the safety of TMP-SMX single dose or two dose oral challenges in predominantly non-HIV-infected patients with "sulfa" antibiotic allergy labels that were inconsistent with severe delayed cutaneous reactions. We show that 89% of patients with a TMP-SMX allergy and 98.9% of those with an unspecified "sulfa" antibiotic label can safely receive a single or two dose oral TMP-SMX challenge. Further, in patients who undergo future treatment with TMP-SMX after challenge, the majority (83%) will tolerate it uneventfully, and for those with a reaction on oral challenge, they experience only mild symptoms. In the past, desensitization or multiple dose graded challenge has been the proposed strategy for patients who had a need for sulfa antimicrobials. Our study supports TMP-SMX single dose or graded 2-dose oral challenge as a safe, pragmatic, efficacious approach to the patient with a non-severe delayed reaction history, which is the most common clinical phenotype associated with TMP-SMX, or a non-severe immediate reaction history who is labeled as "sulfa allergic."

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Figure Legends:

Figure 1: Flowchart of the study. Choice of challenge (single-dose or two-dose) was determined by reaction history. Abbreviations: DHR= drug hypersensitivity reaction; HIV= human immunodeficiency virus; TMP-SMX= trimethoprim-sulfamethoxazole

Table 1. Characteristics of patients undergoing single and two dose TMP-SMX oral challenge, and the outcome of that challenge

	Total N or Median [IQR]	Passed Oral TMP-SMX Challenge No. (% Total) or Median [IQR]	Failed Oral TMP-SMX Challenge No. (% Total) or Median [IQR]	p-value
Total no. of patients	204	191 (93.6)	13 (6.4)	
Age	62 [48, 70]	62 [50, 70]	48 [31, 61]	0.03
Time since reaction in years (**n=167, with n=37 missing)	20 [9, 39]	20 [10, 40]	3 [1, 10]	<0.0005
Sex				
Female	162	151 (93.2)	11 (6.8)	0.48
Male	42	40 (95.2)	2 (4.8)	
Race				
White	188	177 (94.1)	11 (5.9)	0.32
Black	9	8 (88.9)	1 (11.1)	
Unknown	5	4 (80.0)	1 (20.0)	
Asian	2	2 (100.0)	0	
Index reaction history				
Delayed symptoms	106	97 (91.5)	9 (8.6)	0.03
Unknown	75	74 (98.7)	1 (1.3)	
Immediate symptoms	23	20 (87.0)	3 (13.0)	
Indication for Consult				
Multi-drug allergy	139	131 (94.2)	8 (5.8)	0.10
Anticipated need for treatment	41	40 (97.6)	1 (2.4)	
Need for prophylaxis	19	16 (84.2)	3 (15.7)	
Infection without other options	5	4 (80.0)	1 (20.0)	
Co-Morbidities				
Non-HIV infected	195	184 (94.3)	11 (5.6)	0.11
HIV infected	9	7 (77.8)	2 (22.2)	
No Diabetes	166	155 (93.3)	11 (6.7)	0.55
Diabetes	38	36 (94.7)	2 (5.3)	
No Transplant	187	175 (93.6)	12 (6.4)	0.70
Transplant	17	16 (94.1)	1 (5.9)	
Nature of initial label				
Trimethoprim-sulfamethoxazole	109	97 (89.0)	12 (11.0)	0.003
Unspecified sulfa with ongoing avoidance of trimethoprim-sulfamethoxazole	95	94 (98.9)	1 (1.1)	
Type of challenge (selected/dependent upon index reaction history)				
Single dose	179	171 (95.5)	8 (4.5)	0.01
Two dose	25	20 (80.0)	5 (20.0)	

Comparisons between passage versus failure of oral challenge stratified by categorical predictors was performed using two-sided Fisher's exact test. Comparisons between continuous predictors was performed using two-sided Wilcoxon rank-sum test.

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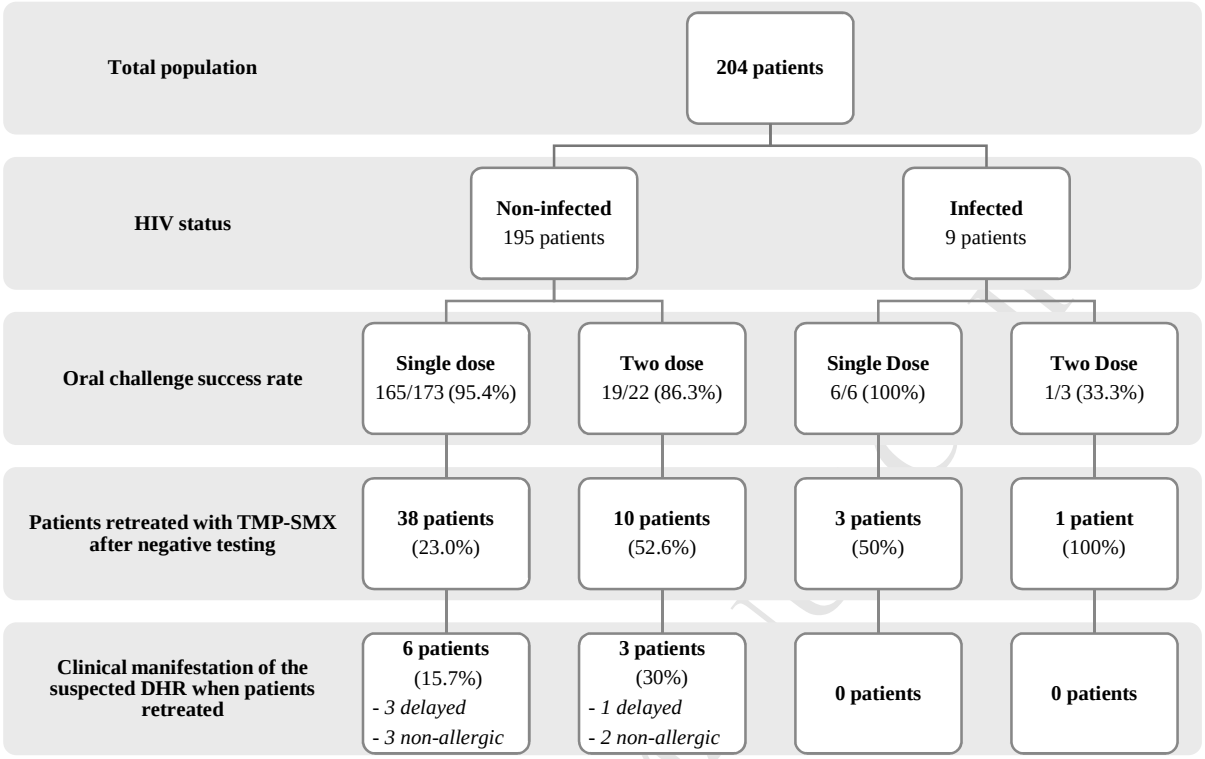

Table E1. Criteria for single or two dose TMP-SMX oral challenge and exclusion

Challenge Type	Criteria	Dose(s)	Follow-up
Single Dose	Non-severe delayed reactions without multiple features consistent with IgE mediated reaction Non-severe immediate (e.g. isolated urticaria, maculopapular rash, or gastrointestinal symptoms) reaction (< 1 hour) greater than 5 years ago Non-severe accelerated reaction (> 1 hour to < 36 hours) greater than 5 years ago Unknown, remote history	TMP-SMX 80-400mg	2 hour observation in clinic after full dose 24 hour phone call after full dose
Two Dose	Non-severe immediate reaction (< 1 hour) within the past 5 years Non-severe accelerated reaction (> 1 hour but < 36 hours) within the past 5 years Anaphylaxis at any time point in the past Multiple (2 or more) features potentially compatible with IgE mediated reaction at any time point in the past • Urticaria • Angioedema • Shortness of breath • Hypotension Significant patient anxiety surrounding single dose challenge	TMP-SMX 8-40mg TMP-SMX 80-400mg	1 hour observation in clinic after first dose 2 hour observation in clinic after second, full dose 24 hour phone call after second, full, dose
Excluded	Stevens-Johnson syndrome Toxic epidermal necrolysis Drug rash with eosinophilia and systemic symptoms Acute generalized exanthematous pustulosis Drug induced nephritis Drug induced hepatitis		

Table E2. Clinical manifestation of drug hypersensitivity in patients who failed a direct oral challenge to TMP-SMX

Patient no.	Index Reaction	Time from Index Reaction (years)	HIV status	Challenge Type (dose)	Symptom	Time to reported DHR (days)	DHR type
1	Delayed	2	Negative	Single	Rash starting 6 to 8 hours after challenge	0	Delayed
2	Delayed	1	Negative	Single	Erythema of the face, neck, chest, and abdomen 8 hours after challenge	0	Delayed
3	Delayed	?	Negative	Single	Pruritus 30 minutes after challenge dose	0	Immediate
4	Unknown	?	Negative	Single	Urticaria	1	Delayed
5	Delayed	9	Negative	Single	Pruritus 10 minutes after challenge dose	0	Immediate
6	Delayed	9	Negative	Single	Low-grade fever, headache, and myalgias without rash 6 hours after challenge	0	Delayed
7	Immediate	1	Negative	Two	Urticaria 15 minutes after taking second challenge dose	0	Immediate
8	Immediate	10	Negative	Single	Urticaria 30 minutes after challenge dose	0	Immediate
9	Delayed	14	Negative	Two	Fever, nausea, vomiting 2 hours after second challenge dose; required observation admission	0	Delayed
10	Delayed	3	Positive	Two	Left arm pain and malaise without fever or rash 30 minutes after second challenge dose	0	Immediate
11	Delayed	15	Negative	Single	Fever without rash 1 hour after challenge dose	0	Immediate
12	Immediate	0	Negative	Two	Throat itching and chest tightness 30 minutes after second challenge dose	0	Immediate
13	Delayed	0	Positive	Two	Flushing of skin 2 hours after second challenge dose	0	Delayed

Table E3. Characteristics of patients that underwent two step oral TMP-SMX challenge

Patient no.	Index Reaction Characterization	Symptoms of Index Reaction	Time from Index Reaction (years)	Nature of initial label	HIV status	Challenge Outcome
1	Delayed	Urticaria and face/lip swelling after 7 days	0	TMP-SMX	Negative	Passed
2	Delayed	Swelling of hands/feet after 12 hours	45	Unspecified sulfa	Negative	Passed
3	Delayed	Maculopapular rash, fever	?	Unspecified sulfa	Negative	Passed
4	Immediate	Urticaria, shortness of breath*	38	Unspecified sulfa	Negative	Passed
5	Immediate	Urticaria, angioedema, shortness of breath*	47	Unspecified sulfa	Negative	Passed
6	Delayed	Urticaria after 7 days	1	TMP-SMX	Negative	Passed
7	Delayed	Urticaria after 14 days	1	TMP-SMX	Negative	Passed
8	Delayed	Maculopapular rash after 2 days	11	TMP-SMX	Negative	Passed
9	Delayed	Shortness of breath, throat swelling after 2 days	15	Unspecified sulfa	Negative	Passed
10	Delayed	Urticaria and facial swelling after 12 hours	27	Unspecified sulfa	Negative	Passed
11	Delayed	Urticaria 2 years into taking for PJP prophylaxis	25	TMP-SMX	Positive	Passed
12	Immediate	Urticaria	1	TMP-SMX	Negative	Failed
13	Delayed	Urticaria after several doses	8	TMP-SMX	Negative	Passed
14	Delayed	Fever, nausea, vomiting, and hypotension after second dose	14	TMP-SMX	Negative	Failed
15	Delayed	Urticaria after third dose	20	TMP-SMX	Negative	Passed
16	Immediate	Anaphylaxis (urticaria, shortness of breath)	47	Unspecified sulfa	Negative	Passed
17	Delayed	Fever, arm pain, vomiting, and malaise after two days	3	TMP-SMX	Positive	Failed
18	Delayed	Urticaria after third dose	12	TMP-SMX	Negative	Passed
19	Immediate	Shortness of breath, chest tightness*	0	TMP-SMX	Negative	Failed
20	Delayed	Urticaria, lip swelling after 5 days of PJP prophylaxis	0	TMP-SMX	Positive	Failed
21	Immediate	Throat tightness, palpitations	15	Unspecified sulfa	Negative	Passed
22	Delayed	Urticaria, face/lip/tongue swelling after three days	0	TMP-SMX	Negative	Passed
23	Unknown	Reaction within 1 day	6	TMP-SMX	Negative	Passed
24	Immediate	Anaphylaxis (no symptom description available)	?	TMP-SMX	Negative	Passed
25	Immediate	Urticaria, lip swelling	1	TMP-SMX	Negative	Passed

* = Patients with potential immediate histories that could have been compatible with anaphylaxis as characterized by immediate reactions with multisystem involvement but not clearly defined as anaphylaxis on chart review

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Table E4. Symptoms attributed to TMP-SMX during subsequent courses of treatment which led to cessation of treatment

Patient no.	**Symptom**	**Time to DHR (days)**	**DHR characterization**	**Stopped Treatment**
1	Nausea	3	Non-allergic	Yes
2	Rash (tolerated 3 retreatment courses previously)	2	Delayed	Yes
3	Mouth ulcers (tolerated 7 retreatment courses previously)	1	Delayed	Yes
4	Rash	10	Delayed	Yes
5	Back pain	7	Non-allergic	Yes
6	Mouth and lip tingling	2	Non-allergic	Yes
7	Rash	6	Delayed	Yes
8	Cough	7	Non-allergic	Yes
9	Shortness of breath	5	Non-allergic	Yes

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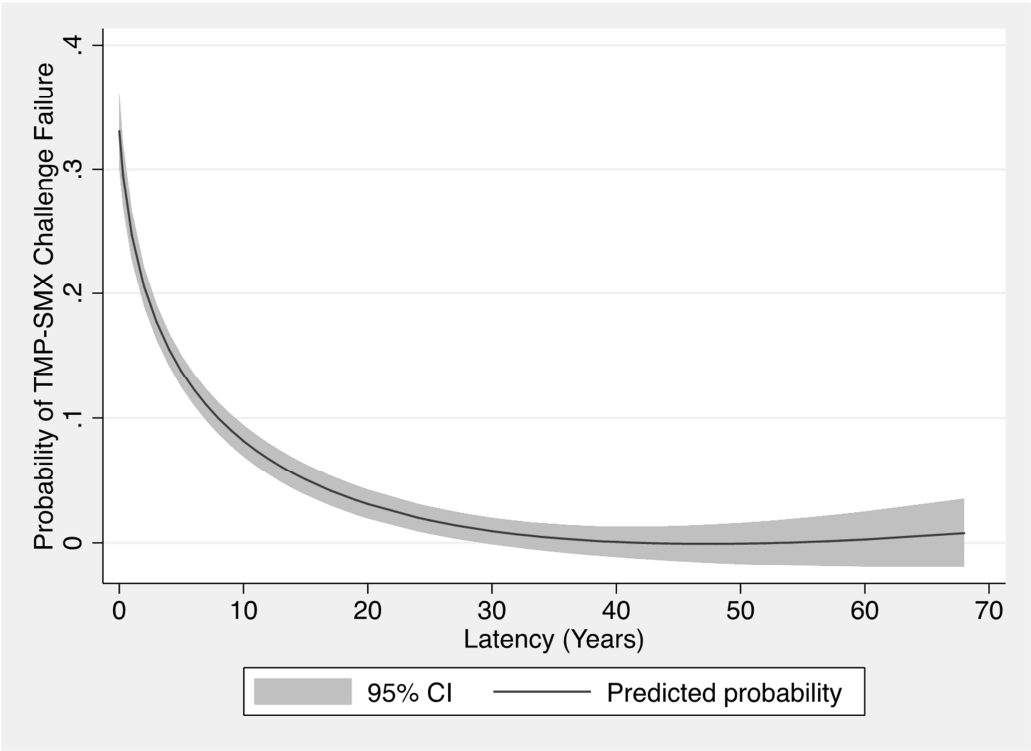

Figure E1: Probability of oral challenge failure and time from index reaction (years) in a logistic model adjusted for age, sex, ethnicity, HIV status, and index reaction history.
Abbreviations: TMP-SMX= trimethoprim-sulfamethoxazole