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## The SUS and the Triad of Urban Arboviruses (2015-2020): Essay about the Inevitable Correlation between Public Health and Society

By Vanessa De Jesus Queiroz

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**Abstract-** This essay analyzes the links between the Sistema Único de Saúde (SUS) and the different social scopes, from reflections about the presence of three arboviruses transmitted by *Aedes Aegypti*: Dengue, Chikungunya and Zika. This text is more social history approach than an analysis of specific biological and pathological aspects related to each of these diseases. The concepts of Space of Experience and Horizon of Expectation, as proposed by Reinhart Koselleck, are used to support the argument that defends the importance of SUS in recently and in the future. Furthermore, we also present the concept of Inevitable Correlation, proposed by us as essential to a theoretical-methodological approach concerned with investigating objects of historical problematization in a network perspective that fundamentally interconnects them. We start from the hypothesis that thinking about SUS, one of the main foundations of public health in Brazil, involves considering the network of people and institutions that coexist with it.

**Keywords:** *SUS, inevitable correlation, urban arbovirus, public health, Brazil.*

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# The SUS and the Triad of Urban Arboviruses (2015-2020): Essay about the Inevitable Correlation between Public Health and Society

O SUS E A Tríade De Arboviroses Urbanas (2015-2020): Ensaio Sobre A Correlação Inevitável Entre Saúde Pública E Funcionamento Social

Vanessa De Jesus Queiroz

**Resumo-** Este ensaio aborda as relações entre o Sistema Único de Saúde (SUS) e diferentes esferas sociais a partir de reflexões sobre a vigência de três arboviroses transmitidas pelo *Aedes Aegypti*. *Dengue*, *Chikungunya* e *Zika* Vírus. O intuito deste texto é mais uma análise do ponto de vista histórico-social do que sobre aspectos biológicos e patológicos relativos à cada uma delas. Os conceitos de Espaço de Experiência e Horizonte de Expectativa, conforme propostos por Reinhart Koselleck, são utilizados para embasar o argumento que defende a importância do SUS no agora e no futuro. Ademais, também apresentamos o conceito de correlação inevitável, por nós proposto como essencial à uma abordagem teórico-metodológica preocupada em investigar objetos da problematização histórica numa perspectiva de rede que os interliga fundamentalmente. Partimos da hipótese de que pensar sobre o SUS, um dos principais alicerces da saúde pública no Brasil, envolve considerar a rede de pessoas e instituições que com ele coexistem. A tríade de arboviroses no espaço de experiência entre 2015 e 2020 se caracteriza como um, dentre os muitos possíveis, exemplos de que a defesa do SUS deve fazer parte do horizonte de expectativa em nome da garantia de um dos principais direitos sociais de que a população brasileira desfruta há algumas décadas: o acesso gratuito à saúde.

**Palavras-Chave:** SUS, correlação inevitável, arboviroses urbanas, saúde pública, Brasil.

**Abstract-** This essay analyzes the links between the Sistema Único de Saúde (SUS) and the different social scopes, from reflections about the presence of three arboviruses transmitted by *Aedes Aegypti*. *Dengue*, *Chikungunya* and *Zika*. This text is more social history approach than an analysis of specific biological and pathological aspects related to each of these diseases. The concepts of Space of Experience and Horizon of Expectation, as proposed by Reinhart Koselleck, are used to support the argument that defends the importance of SUS in recently and in the future. Furthermore, we also present the concept of Inevitable Correlation, proposed by us as essential to a theoretical-methodological approach concerned with investigating objects of historical problematization in a network perspective that fundamentally interconnects them. We start from the hypothesis that thinking about SUS, one of the main foundations of public health in Brazil, involves considering the

network of people and institutions that coexist with it. The triad of arboviruses in the space of experience between 2015 and 2020 is characterized as one among many possible ones, example of which the defense of SUS should be part of the horizon of expectations as a guarantee of one of the main social rights that the Brazilian population has enjoyed for a few decades: free access to health.

**Keywords:** SUS, inevitable correlation, urban arbovirus, public health, Brazil.

## I. PONTO DE PARTIDA

No dia 27 de outubro de 2020 foi publicado, no Diário Oficial da União do Brasil, o texto do Decreto n. 10.530, de 26 de outubro de 2020, que versava sobre a “modernização e a operação de Unidades Básicas de Saúde dos Estados, do Distrito Federal e dos municípios”, a partir da autorização de estudos que possibilitassem a participação da iniciativa privada na administração destes órgãos da saúde pública. Noutras palavras, o dispositivo legislativo abria margem para a privatização da gestão das Unidades Básicas de Saúde (UBSs), por vezes popularmente chamadas de postos de saúde. Estes estabelecimentos são responsáveis pelo atendimento gratuito a problemas que não necessariamente precisam ser resolvidos no atendimento emergencial dos hospitais. As UBSs executam, ainda, o serviço de encaminhamento para tratamento especializado em nosocômios. Assim sendo, colaboram ao combate à superlotação dos hospitais públicos – que é um grave problema do sistema de saúde pública brasileiro atual, e ainda fornecem gratuitamente atendimentos imediatos, como a distribuição de remédios e preservativos, aplicação de vacinas, odontologia, primeiros socorros, orientação preventiva e vários outros à população.

O texto do Decreto n. 10.530 circulou em diversos meios de comunicação, sobretudo nos veículos on-line, o que causou debates e grande reação popular e político-partidária contra uma possível privatização do Sistema Único de Saúde (SUS), do qual as Unidades Básicas de Saúde fazem parte e são porta de entrada. Um dos principais argumentos propagados

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era o de que a parceria com iniciativas privadas na administração das UBSs abriria caminhos para que outras competências do Sistema Único fossem privatizadas, o que ameaçaria o acesso gratuito à saúde, garantido pela Constituição Federal de 1988. As resistências resultaram no Decreto n. 10.533, de 28 de outubro de 2020, que revogou aquele publicado dois dias antes. Ainda que em âmbito oficial os dispositivos do decreto de 26 de outubro tenham sido suspensos junto à sua revogação, os debates sobre a privatização perduram nas diversas esferas sociais e políticas.

O Decreto 10.530 e sua rápida supressão levantaram discussões acerca do direito a um sistema único e público de saúde. Estas diretamente relacionadas a outros motes das esferas sociais, culturais, econômicas e políticas da sociedade brasileira e da história da saúde pública do país até aqui. Neste ensaio, que se posiciona em defesa do SUS, abordaremos uma, dentre muitas, das questões que conectam saúde pública a várias outras facetas do funcionamento social, a partir da relação entre o Sistema Único de Saúde e três das mais preocupantes doenças transmitidas pelo *Aedes Aegypti* – *Dengue*, *Zika* e *Chikungunya*. Mais do que uma análise detalhada sobre os prejuízos e definições estritamente biológicas sobre estas moléstias, trata-se de considerações do ponto de vista da história social, preocupada em compreender conexões, diálogos e conflitos envolvidos nas ações e convivências humanas ao longo do tempo.

Nosso objetivo central pode ser definido pela pergunta: Como a tríade de arboviroses transmitidas pelo *Aedes Aegypti* nos ajuda a pensar o SUS e a saúde pública no Brasil? Em torno desta problematização, adotamos um caminho metodológico de investigação de variadas fontes escritas, a exemplo de marcos legislativos e boletins da saúde pública do Ministério da Saúde, com vistas a verificar o panorama que esses documentos nos mostram acerca do tema, mas também para refletir brevemente sobre limites inerentes ao trabalho histórico com estes documentos, que são proposital e seletivamente pensados e construídos por sujeitos em condições de produção específicas. Trata-se do cuidado metodológico com o trabalho de fontes escritas, que implica avaliar que junto à produção de informações ocorre a produção de silêncios. Quanto ao recorte temporal, falamos dos anos de 2015-2020, que correspondem aproximadamente a ascensão do grande surto de *Zika* Vírus, considerado situação de emergência nacional de saúde pública no Brasil, até o ano de lançamento dos dois decretos sobre a possível privatização das UBSs, ano em que também ocorre o início da grave pandemia de Coronavírus SARS-CoV-2 como mais um desafio ao SUS.

Como fundamentos teóricos-metodológicos de nosso texto, elegemos três conceitos principais. Os dois primeiros são os de *espaço de experiência* e

*horizonte de expectativa*, legados de Reinhart Koselleck (2006). Visto que o espaço de experiência se relaciona com um tipo de passado atual, onde ocorrem constantes atualizações presentes de experiências vividas, evocamos esta categoria para pensar nos problemas enfrentados pela saúde pública, causados pela tríade de enfermidades aqui analisada, com ênfase nas relações entre SUS, população e Estado. Trata-se de ponderar sobre quais sentidos o referido sistema tem adquirido na experiência social com a saúde como bem público de acesso gratuito. Como aponta Koselleck (2006), o conceito de espaço de experiência aparece como indissociável da noção de horizonte de expectativa. Esta se refere a possibilidades e intenções ulteriores, ao que ainda não foi vivenciado, portanto não se encontra no espaço de experiência, mas neste se embasa para projeções futuras possíveis. Aqui utilizamos este conceito para evidenciar, a partir do espaço de experiência com a saúde pública no Brasil entre 2015 e 2020, a coerência de argumentos que alocam o SUS como necessário a um horizonte de expectativa que preconiza uma satisfatória situação de saúde pública no país. Por fim, apresentaremos o conceito de *correlação inevitável*, por nós proposto como noção que trata de entender que a escolha de uma esfera de problematização histórica implica, obrigatoriamente, a consideração de outras esferas com as quais o objeto central da problematização mencionada divide espaço. Logo veremos que investigar sobre o SUS entre 2015-2020 envolve, fundamentalmente, examinar aspectos da sociedade onde o mesmo está inserido.

Com base nos objetivos esclarecidos acima, este ensaio está dividido em três tópicos principais. O primeiro faz um histórico do SUS a partir de seus marcos legais e contextualiza sua ascensão, bem como elucida limites das legislações que o regem desde sua criação até os dias atuais. O segundo expõe dados sobre as arboviroses no intuito de refletir sobre sua presença e impactos que elas ocasionam à saúde pública, para evidenciar a necessidade do SUS ao funcionamento social, bem como pensar as moléstias transmitidas pelo *Aedes Aegypti* como desafio e elo entre saúde, sociedade e Estado. Na terceira parte do texto, prosseguimos com a análise da correlação inevitável entre SUS, sociedade e Estado, com reflexões que a exemplificam. Nas considerações finais, além de conclusões sobre a presença da tríade do mosquito, breves ponderações sobre a atual pandemia de COVID-19 enfrentada pelo Sistema Único de Saúde, Estado e população, também são lançadas.

#### a) *Sistema Único de Saúde: breve histórico e problematização*

A saúde é direito de todos e dever do Estado, garantido mediante políticas sociais e econômicas que visem à redução do risco de doença e de outros agravos e ao

acesso universal e igualitário às ações e serviços para sua promoção, proteção e recuperação (CF, 1988, art.196)

O artigo faz parte da Carta Magna que define direitos e deveres garantidos da sociedade brasileira. Ele e os demais pontos da seção de saúde da Constituição Federal Brasileira de 1988 consolidam o acesso gratuito à saúde como dever do Estado e direito da população. Também apresentam a ideia de um sistema único de saúde como principal garantidor do referido direito. A previsão desse tipo de sistema na Constituição resulta de uma série de fatores sociais antecedentes. Jaime Bellido *et al.* (2018), autores com os quais corroboramos, apontam como importante para contextualização o período entre a criação do Instituto Nacional de Previdência Social (INPS), em 1966, e a Reforma Sanitária, a partir de 1970.

Com a ascensão do INPS, a configuração sistemática de acesso à saúde voltava-se à centralização financeira e administrativa. A concentração de recursos na previdência social, conforme apontam os autores (BELLIDO *et al.*, 2018:1752), formulava um sistema de saúde focado em fornecer serviços médicos como parte da previdência social aos trabalhadores por ela assegurados. Privilegiava-se o serviço de saúde privado, a partir da existência de um acordo que isentava empresas privadas que garantissem esses serviços de saúde aos seus funcionários do imposto de contribuição à previdência. É importante perceber que neste momento no mínimo dois tipos de convênio ocorriam. O primeiro entre o Governo Federal e as empresas. Se estas garantissem os serviços médicos aos seus funcionários, ajudando o Estado na efetivação da ideia de previdência social, estariam livres de pagar impostos de contribuição à previdência. Para o segundo, entre os empregadores e o setor privado de saúde conveniado, a parceria era benéfica para que os primeiros garantissem sua isenção de impostos e o último pudesse ganhar clientela e visibilidade.

A década de 1970 marca o surgimento do Movimento Sanitário (ou Reforma Sanitária), que propagava a ideia de que o sistema de saúde deveria ser reformado com base numa nova perspectiva, que não mais preconizasse o lado puramente biológico dos problemas de saúde, mas considerasse sua faceta histórica e sociocultural (IBIDEM). Na perspectiva reformista, o Estado ganharia papel mais central e direto na garantia de acesso à saúde, como parte de um processo maior e mais democrático de redução da desigualdade social pela ótica dos serviços de saúde como necessidade pública.

Com o pós-ditadura civil militar, o cenário de esforços movido pelo ideal de democratização tem fundamental expressão na Constituição Federal de 1988. Parte das demandas do Movimento Sanitário é atendida pela presença da saúde pública de acesso

gratuito como direito assistido pela Carta Magna. Com isto, o Estado assume a responsabilidade dos serviços de saúde gratuitos para além do Ministério da Previdência Social. É importante destacar que a ascensão de um sistema único de saúde não desmonta a saúde privada, mas com ela divide espaço, muitas vezes firmando acordos, conforme prevê o parágrafo 1º, do art. 199 da Constituição de 1988, que dispõe que “As instituições privadas poderão participar de forma complementar do Sistema Único de Saúde, segundo diretrizes deste (...)”.

Além da Carta Magna de 1988, dois dispositivos legais são importantes para pensar sobre o histórico de criação do SUS. São eles: as Leis n. 8.080, de 19 de setembro de 1990 e n. 8.142, de 28 de dezembro de 1990. A primeira versa sobre “as condições para a promoção, proteção e recuperação da saúde, a organização e o funcionamento dos serviços correspondentes e dá outras providências”. Esta regula as ações de saúde em todo o território nacional, definindo objetivos e atribuições estaduais, municipais e distritais para garantia das saúdes física e mental, princípios do SUS, suas diretrizes e política de gestão, assistência e funcionamento e, além disso, define outras disposições, a exemplo de vigilância sanitária e epidemiológica, saúde do trabalhador, meio ambiente, pesquisas sobre saúde e tecnologia, entre outros. A Lei n. 8.142, de 28 de dezembro de 1990 dispõe “sobre a participação da comunidade na gestão do Sistema Único de Saúde (SUS) e sobre as transferências intergovernamentais de recursos financeiros na área da saúde e dá outras providências”. Grosso modo, esta legislação regula a hierarquia de cargos e órgãos envolvidos na administração do SUS, dispondo, também, sobre deveres de cada um para obtenção de recursos governamentais para fomento da saúde pública.

Outros dispositivos legais, inclusive mais atuais, poderiam ser citados, a exemplo da Lei n. 12.845 de 1º de agosto de 2013, que determina que os hospitais públicos devem fornecer atendimento com todos os serviços necessários às vítimas de violência sexual, ou a Lei n. 13.427 de 30 de março de 2017, que altera a Lei n. 8.080, de 19 de setembro de 1990, para incluir “o princípio da organização de atendimento público específico e especializado para mulheres e vítimas de violência doméstica em geral”. Contudo, ainda que as referidas leis evidenciem que o SUS acompanha as necessidades e transformações sociais ao longo do tempo, aqui buscamos apenas apresentar alguns dispositivos fundamentais para refletir sobre seu histórico de criação.

Mais do que apenas apontar os marcos legais da institucionalização do Sistema, devemos problematizá-los, com vistas a compreender ideias como a de saúde pública e Sistema Único de Saúde como objetos históricos, permeados por negociações,



falhas e conflitos ao longo do tempo. Propomos algumas considerações principais para pensar o SUS e suas legislações reguladoras desde sua criação até aos dias atuais. A primeira é que ele não surge do nada. Sua criação faz parte de um processo gradual de significações e ressignificações da ideia de saúde e do papel do Estado como provedor do bem estar social. Sua fundação, com a prerrogativa central de garantia de acesso público aos serviços de saúde, faz parte de um movimento maior que ocorria no Brasil, recém saído de um período ditatorial e que buscava a redemocratização. Parte dos esforços em nome deste ideal envolvia a redução das desigualdades sociais. O Sistema Único de Saúde surge no sentido de considerar essas desigualdades também no campo da saúde pública. Como afirmam Jaime Bellido *et al.* (IBIDEM) o contexto torna "imperativa a democratização do acesso à saúde e a reestruturação do sistema de serviços".

Do ponto de vista da teoria da história, aqui podemos evocar o conceito de espaço de experiência, com a consideração do SUS como parte da demanda social pela redemocratização da sociedade de finais da década de 1980 e início de 1990. Ademais, podemos considerar os marcos legislativos que o regulam como parte do horizonte de expectativa para seu funcionamento – o texto da Constituição previa como o SUS deveria funcionar, mas o funcionamento de fato ainda não era parte do espaço de experiência quando o texto constitucional foi redigido. É importante ressaltar que a ideia de horizonte de expectativa não é algo imutável e uno. Existem problemas presentes ao se pensar na existência e atuação do SUS, como desvios de planejamento na aplicação prática e limites das leis.

A ascensão de um Sistema Único de Saúde e a garantia de acesso gratuito aos serviços oferecidos não ocorrem de forma imediata, completamente eficaz e homogênea. O SUS envolve uma rede de pessoas e órgãos, conflitos e acordos. A administração da saúde pública em todo o território nacional abarca diferentes instâncias governamentais para tratar dos hospitais e demais aparatos do Sistema em âmbitos regionais, distritais, estaduais e federais. No âmbito nacional/federal o Ministério da Saúde é o órgão gestor, no estadual e no municipal, as secretarias de saúde correspondentes. Problemas de gestão, corrupção, insuficiência, burocracia e outros são esperados nesse tipo de serviço abrangente que implica necessariamente, um comando cooperativo. Ademais, os diferentes perfis populacionais de cada região ou estado atendido pelo SUS varia. Esta variação é, por vezes, responsável pela alteração de planos orçamentários nem sempre atendidos, ocasionando a escassez de recursos materiais e humanos. A superlotação dos hospitais públicos, que é um problema há alguns anos no Brasil, evidencia a assertiva.

A tarefa de pensar os limites do SUS não se restringe apenas ao escopo da falta de recursos. Cabe-nos refletir, de igual modo, sobre a existência da iniciativa privada e outros elementos. A garantia de acesso gratuito aos serviços de saúde não significa, na prática, que todas as pessoas o procurem. Muitos empregadores optam por ofertar planos de saúde como benefício trabalhista. Para muitas empresas é benéfico contratar planos de saúde coletivos para seus funcionários, seja pela atratividade que o item oferece ao cargo e consequente bom status da empresa, seja pela isenção de impostos ou por outras razões. Uma parcela social, apesar do direito, não desfruta do acesso público à saúde por opção, ainda que para alguns motivos específicos desta escolha este número seja pequeno ao longo dos anos: para 2019, por exemplo, três décadas após a implementação do SUS, dados levantados para a pesquisa nacional de saúde para grandes regiões e unidades da federação no Brasil revelavam que apenas 28,5% da população brasileira tinha plano de saúde e/odontológico (IBGE RJ, 2020:29). Outra causa da escolha de não optar pelo atendimento no Sistema envolve as pessoas que escolhem práticas de cura alternativas (muitos de nós optamos por chás, pela consulta ao farmacêutico ou mesmo por aguardar a ação do tempo ao em vez de procurar um estabelecimento de saúde, não é mesmo?!).

Outro elemento fundamental a se considerar é que a garantia de acesso gratuito por um sistema único de saúde não faz com que a saúde chegue a todos. Relatórios do Conselho Nacional dos Secretários de Saúde (CONASS) e outros veículos de informação apontam a superlotação dos hospitais, muitas vezes causadas pela dificuldade de informação sobre a possibilidade de atendimento de problemas mais simples nas Unidades Básicas de Saúde ou mesmo pela ausência de UBSs, hospitais e recursos em algumas localidades. A sobrecarga dos nosocômios públicos exerce um tipo de efeito dominó que ocasiona a escassez de profissionais, remédios, infraestrutura e outros. A insuficiência de apoio financeiro e logístico por parte do Governo Federal ao longo da história do SUS também deve ser levada em conta, pois é em grande parte responsável pela inexistência de hospitais e unidades de saúde em várias regiões.

A ascensão e o desenvolvimento do Sistema Único de Saúde implicam uma rede de pessoas, de órgãos, de instâncias, leis e outros. As reflexões expostas até aqui podem ser analisadas sobre o conceito de correlação inevitável, visto que é impossível pensar a criação e o desenvolvimento do Sistema Único de forma isolada. O acesso gratuito à saúde envolve legislações, diversos sujeitos sociais, instâncias de governo, instituições científicas, população e outras esferas que tornam saúde pública algo heterogêneo,



uma questão indissociável do funcionamento dos campos sociais, culturais, econômicos e políticos.

Por fim, ressaltamos que apesar de se tratar de um sistema único, o SUS é diverso e oferta variados serviços da saúde profissional– vigilância sanitária/alimentar, clínica médica, clínica cirúrgica, odontologia, pediatria, distribuição de remédios e vacinas, entre outros. Muitas vezes nem todos esses serviços encontram-se disponíveis à toda população- já mencionamos a escassez de recursos, a insuficiência do apoio governamental, a superlotação de hospitais e localidades que não contam com unidades de saúde. Ainda que alguns dos problemas descritos pareçam comuns a diferentes décadas, não se deve perder de vista que transformações ocorrem longo do tempo, obedecendo a questões contextuais diversas. No período de escrita deste ensaio, 2020-2021, por exemplo, vivenciamos uma excepcionalidade que mudou muitos aspectos de nossa relação com o governo e com o SUS: a pandemia de COVID-19. Além das questões aqui já ressaltadas, as epidemias e pandemias que grassam no Brasil, único país que possui um sistema único de saúde, afetam diretamente seu funcionamento. As moléstias em grandes proporções tanto dificultam sua efetividade, como demonstram sua necessidade. É sobre isso que trataremos no tópico a seguir.

#### b) *Arboviroses Urbanas entre 2015 e 2020: Dengue, Zika e Chikungunya*

*Dengue, Zika e Chikungunya* são arboviroses<sup>1</sup> urbanas transmitidas pelo *Aedes Aegypti*, mosquito rajado da espécie *Culicidae*, que depende da concentração humana em uma localidade para assentar morada. Machos e fêmeas se alimentam de néctar, seiva e outras substâncias que contêm açúcar. Contudo, a fêmea precisa da ingestão de sangue para a produção de ovos. Desse modo, a transmissão dos arbovírus ao ser humano é feita pelo espécime feminino. Este pode infectar mais de uma pessoa por lote de ovos, devido a uma característica chamada discordância gonotrófica. Ambientes com água parada, limpa ou suja, são os mais propícios para colocação dos ovos da fêmea e consequente reprodução destes insetos. Neste ensaio preconizamos três arboviroses, mas é válido lembrar que o *Aedes Aegypti* também pode transmitir a febre amarela urbana.

Ainda que as primeiras descrições científicas sobre o mosquito datem da década de 1760, onde foi primeiramente descrito como *Culex Aegypti*, as primeiras ocorrências laboratorialmente documentadas do vírus da *Dengue* - doença mais popular transmitida pelo espécime no Brasil-, foram registradas na década de 1980, surgidas em Roraima em 1981-1982, tendo se

manifestado epidemicamente no Rio de Janeiro e algumas regiões do Nordeste em 1986 (IOC, 2020<sup>2</sup>). Mas a história da saúde pública brasileira com o mosquito começou antes da popularização da relação entre ele a *Dengue*. Em 1958, a Organização Mundial da Saúde reconheceu o Brasil como livre do vetor. Isto foi possível após rigorosas medidas de combate ao mosquito, visto como transmissor da febre amarela urbana. A perda de rigor das medidas sanitárias de combate adotadas somadas ao movimento de circulação de pessoas por diferentes lugares do mundo, são crucial parte da explicação para a reintrodução do mosquito no país.

Segundo Denise Valle e Aparecida Braga (2007:113), desde 1980 “iniciou-se um processo de circulação viral, com epidemias explosivas que atingiram todas as regiões brasileiras”. Segundo texto da OMS (2019), a *Dengue*, hoje principal doença relacionada ao mosquito, “é generalizada ao longo dos trópicos, com variações locais de risco influenciadas pela precipitação, temperatura e rápida urbanização não planejada” e sua incidência tem crescido exponencialmente em todo o mundo com o passar dos anos. A título de ilustração da presença e crescimento da arbovirose no Brasil, apresentaremos alguns números ao longo do período aqui analisado. Dizemos alguns porque os dados variam conforme período de produção e publicação dos documentos consultados e os números são aproximados, visto que muitas incidências não foram oficialmente registradas.

Para 2015, segundo o Boletim Epidemiológico (BE.) n.44/volume 46 da Secretaria de Vigilância em Saúde do Ministério da Saúde, foram registrados 1.587.080 casos prováveis<sup>3</sup> de *Dengue* no Brasil até 05 de dezembro<sup>4</sup>. Para 2016, até 31 de dezembro, o BE. n.45/volume 48 de 2017 apontava a quantia de 1.483.623 casos prováveis. Para 2017, até 16 de dezembro, o mesmo boletim registrava a quantia de 249.056 casos prováveis. Para 2018, até 08 de dezembro, o BE. n.59/volume 49, marcava a cifra de 247.393 casos prováveis. Para 2019, diversos jornais<sup>5</sup> noticiavam o alerta do Ministério da Saúde para o

<sup>2</sup> A matéria de onde extraímos a informação, intitulada “O mosquito *Aedes aegypti* faz parte da história e vem se espalhando pelo mundo desde o período das colonizações”, não menciona data de publicação. Assim sendo, por questões formais, convencionamos o ano em que acessamos o texto como aquele a ser colocado na referência.

<sup>3</sup> “Os casos prováveis são os casos notificados, excluindo-se os descartados, por diagnóstico laboratorial negativo, com coleta oportuna ou diagnosticados para outras doenças” (MS, BOLETIM EPIDEMIOLÓGICO 45, volume 48:1).

<sup>4</sup> Os boletins adicionam às estatísticas a variável “semana epidemiológica”. Para fins de clareza, aqui optamos por indicar apenas os períodos e as datas finais dos mesmos. O calendário epidemiológico pode ser facilmente consultado em portais virtuais do Ministério da Saúde.

<sup>5</sup> A exemplo da coluna de Saúde do *Estado*, da *Folha de São Paulo*, do *Portal UOL*, entre outras.

<sup>1</sup> Arboviroses são doenças transmitidas por arbovírus, classificação que abrange os vírus transmitidos por artrópodes (insetos e aracnídeos).

crescimento do número de casos prováveis para aproximadamente 1,5 milhão. O BE. n. 22/volume 50, de setembro de 2019, mostrava 1.439.471 casos prováveis naquele ano. Para 2020, até 19 de setembro, o número de casos prováveis registrados chegava a 931.903, segundo o BE. n.41/volume 51.

Conforme evidenciam os dados, a *Dengue* tem sido grave problema a ser controlado no Brasil. Logo veremos que o SUS é fundamental à tal tarefa. Antes disso, cabe-nos apresentar mais duas moléstias propagadas pelo *Aedes Aegypti*, que se caracterizam como mais desafios à saúde pública. Nos referimos à Febre *Chikungunya* e ao *Zika Vírus*.

Menos letal, porém com sintomas semelhantes aos da primeira arbovirose, a exemplo de febre alta, dores de cabeça e corporais, manchas na pele e prostrações, chegou ao Brasil, em 2014 ou provavelmente antes<sup>6</sup>, a chamada Febre *Chikungunya* (em Angola: *Catolotolo*). *Chikungunya* significa “aqueles que se dobram” e faz referência ao aspecto físico dos doentes identificados na primeira epidemia documentada entre 1952 e 1953 na Tanzânia. O vírus responsável pela enfermidade é o CHIKV, da família *Togaviridae*. Assim como a *Dengue*, esta febre é transmitida pela picada do *Aedes Aegypti* infectado (O *Aedes Albopictus* também pode espalhar ambas as arboviroses, mas, no Brasil, o principal vetor da transmissão é o *Aegypti*). Diferente da primeira arbovirose de que falamos, ao contrair a *Chikungunya* uma vez, têm-se imunidade para o resto da vida (FIOCRUZ, 2020).

A ascensão da doença no Brasil foi um marco para as pesquisas e políticas públicas em saúde, pois o *Aedes Aegypti* se tornou, em território nacional, vetor de mais uma grave infecção viral em grandes proporções em um momento onde as doenças transmitidas por mosquitos já se apresentavam como alarmante situação. A taxa de mortalidade pela infecção, ainda que menor que a da *Dengue*, potencializou a gravidade. Ainda não existe uma vacina que previna a doença. Assim, a forma de prevenção contra o vírus é o extermínio de criadouros do vetor- este é o método mais eficaz no combate às arboviroses da tríade de que falamos.

Segundo BE. n. 45/volume 48 de 2017, as estatísticas para os primeiros anos<sup>7</sup> de desenvolvimento da *Chikungunya* no Brasil são: para 2015, até 02 de janeiro de 2016, temos o valor de 38.499 casos

prováveis. Para 2016, até 31 de dezembro, foram 277.882 casos prováveis. Para 2017, até o dia 16 de dezembro, os números eram de 185.605 casos prováveis. O BE. n. 59, de 2018, registrava 85.221 prováveis casos para este ano. Para 2019, o BE. n. 22/volume 50 contava 110.627 prováveis casos até 24 de agosto. Por fim, o BE. n. 51/volume 51 apontava a quantia de 58.884 casos prováveis até 27 de junho de 2020.

A *Chikungunya* não foi erradicada no Brasil e também continua a grassar noutros países. A circulação entre pessoas, acompanhada pela concentração dos mosquitos, é um dos fatores que dificultam a erradicação. Ainda que, dentre as três arboviroses, a *Chikungunya* seja a de menor letalidade, outros prejuízos ascendem de sua ocorrência, a exemplo do impacto do grande número de casos superlotar a procura de atendimento nos hospitais do SUS.

Em meados de 2015, com maior ocorrência na região Nordeste e associado ao aumento de casos de microcefalia, o vírus *Zika* foi diagnosticado em terras brasileiras. Desde então, conforme aponta Ilana Löwy (2019), vem se tornando um grande desafio para gestores e profissionais da saúde no Brasil. Um arbovírus, do gênero *Flaviviridae*, chamado ZIKAV é o responsável pela moléstia, majoritariamente transmitida pela picada do *Aedes Aegypti* infectado, mas que também o pode ser por meio de relações sexuais e de mãe para feto<sup>8</sup>. O nome popular, *Zika*, se originou de seu isolamento em 1947, numa região da Floresta tropical *Zika*, em Uganda. De 1954 data a primeira infecção humana descrita na África. Os anos de 2007 e 2013 encabeçaram duas importantes ocorrências registradas do vírus. A primeira na Micronésia, onde grande parte dos infectados não apresentou sintomas; a segunda na Polinésia Francesa, em meio a uma epidemia de *Dengue*. Segundo verbete da Fundação Oswaldo Cruz, entre 2015-2016 o *Zika*-vírus foi epidemia que “representou uma das maiores emergências de saúde pública da história do Brasil”. O contexto, no qual vigorava uma grande epidemia de *Dengue*, tornou-se ainda mais caótico. Mesmo após a chegada de seu fim como ocorrência epidêmica nacional grave, a arbovirose continua sendo objeto de estudos.

O *Zika* é, em grande parte dos casos, assintomático. Quando manifesta sintomas, estes costumam ser mais leves que os da *Dengue*. Entretanto, o vírus pode causar prejuízos à saúde neurológica e nervosa. A síndrome de *Guillain-Barré* é uma de suas consequências mais conhecidas, além da microcefalia em recém-nascidos. Para o Ministério da Saúde o *Zika* é, ainda, uma doença pouco descrita e as

<sup>6</sup> Pesquisadores da Escola de Saúde Pública Mailman, da Universidade de Columbia, e da Fundação Oswaldo Cruz afirmam que o vírus chegou ao Brasil um ano antes do estipulado. Ver: <<https://portal.fiocruz.br/noticia/chikungunya-entrou-no-brasil-um-ano-antes-do-previsto>>. Acesso em janeiro de 2021.

<sup>7</sup> Casos são registrados antes de 2015, conforme evidenciam fontes diversas, a exemplo da pesquisa citada em nota de rodapé anterior. Contudo, obedecendo aos critérios de recorte temporal aqui proposto, apontamos os dados a partir de 2015.

<sup>8</sup> Ver: <<https://portal.fiocruz.br/pergunta/como-ocorre-transmissao-do-virus-zika>>. Acesso em janeiro de 2021.

investigações sobre ela se fundamentam em um número limitado de casos e surtos.

Em 2015, após rumores de uma doença até então incerta que era confundida com rubéola, sarampo, enteovírus, *Dengue* e outras, um pesquisador da Universidade Federal da Bahia finalmente identificou o vírus *Zika*, a partir da coleta de material genético de pessoas portadoras de doença exantemática em Camaçari (BA). Em seguida laboratórios diversos, como o da Fundação Oswaldo Cruz, também perceberam e conduziram investigações sobre a circulação deste agente (MS, 2015). Pesquisadores do setor público e privado, nacional e internacional, foram chamados ao Brasil. A própria diretora da Organização Mundial da Saúde à época, Margareth Chan, viera a terras brasileiras, uma vez que a epidemia de *Zika* era preocupação internacional. Nascimentos de bebês com microcefalia, identificados em mães estrangeiras que quando gestantes haviam estado no Brasil, motivou o decreto da ocorrência do vírus como uma situação de Emergência de Saúde Pública de Importância Internacional pela OMS. O panorama de alerta era agravado pela iminente realização dos Jogos Olímpicos e Para- Olímpicos no país (MS, 2015:23).

Ainda que em 2016 a situação de emergência tenha sido suspensa, a doença continuou e continua a ser objeto de atenção de pesquisas, pois ainda há ocorrência no Brasil e em outros países e se trata de um vírus relacionado à ocorrência de outros males, a exemplo da síndrome de *Guillain-Barré*. Ademais, o pouco tempo desde a confirmação diagnóstica do vírus no Brasil faz com que haja um grande caminho de descobertas científicas pela frente. Quanto às estatísticas, segundo BE. n.45/volume 48 de 2017, em 2016 foram registrados 215.795 possíveis casos até o dia 17 de dezembro. O mesmo boletim mensura 17.338 casos prováveis até 16 de dezembro para o ano de 2017. Para 2018, segundo BE. n. 59/volume 49, foram registrados 8.024 casos prováveis de doenças agudas causadas por *Zika* até 17 de novembro. Até 17 de agosto de 2019, segundo o BE. n.22/volume 50, os números registravam 9.813 casos prováveis. Em junho de 2020, o Centro de Integração de Dados e Conhecimentos para a Saúde da Fiocruz Bahia alertava para o retorno de uma epidemia, por conta da descoberta de uma nova linhagem do ZIKV.

#### c) *As arboviroses para pensar o SUS e o conceito de correlação inevitável*

É fundamental destacar que a frente de controle das arboviroses está majoritariamente sob alçada do Sistema Único de Saúde. As clínicas particulares também atendem pacientes infectados, porém a maior parte da população brasileira e, por conseguinte dos infectados, é atendida pelo SUS, cujos órgãos gestores são também responsáveis pelas

campanhas de comunicação, prevenção e combate ao mosquito vetor.

Evocando o conceito de correlação inevitável, os dados expostos sobre a tríade exigem que os relacionemos a outros aspectos do funcionamento social. Nesse sentido, ainda que um recorte regional específico não seja nosso escopo neste texto, nos cabe esclarecer que diferentes regiões ocupam o ápice da quantia de casos nos diferentes períodos analisados. A título de exemplo, vejamos as estatísticas da *Dengue*. A região Sudeste, mais populosa do Brasil, registrou o maior número de casos prováveis em 2016. Como dissemos há pouco, o *Aedes Aegypti* precisa de concentração humana para se estabelecer. Uma conclusão imediata e pouco cuidadosa pode nos fazer acreditar que a numerosa população de humanos é o principal fator responsável pela liderança nas estatísticas. Contudo, a propagação da referida arbovirose obedece a outros critérios de espalhamento, como a maior presença de recipientes e ambientes com água parada, suja ou limpa. Ainda que locais mais populosos tendam a produzir mais lixo e outras condições favoráveis à proliferação do mosquito, não podemos eleger o volume populacional, de forma isolada, como único motivo das ocorrências. Regiões como Nordeste e Centro-Oeste, menos populosas que a Sudeste, apresentaram expressivo número de casos, com ênfase no ano de 2017, onde manifestaram mais casos prováveis do que a região mais populosa (BE. n. 59/vol. 49 MS, 2018:7).

As relações internacionais e culturais são outro campo indispensável para pensar o impacto das arboviroses e a questão da saúde pública como correlacionada a todo funcionamento social. Exemplo desta afirmação pode ser encontrado no ano de 2014, em que o Brasil foi sede de um importante evento esportivo mundial, a Copa do Mundo de Futebol. Neste ano, a *Dengue* já se caracterizava como algo a ser cuidado pelas autoridades, visto que um país doente não era a imagem desejada em um momento onde as atenções estavam excepcionalmente mais voltadas às terras brasileiras - sobretudo em termos de cobertura televisiva e visitação de turistas estrangeiros.

O ensino, a pesquisa e o próprio saber médico também fazem parte da correlação, porque é no âmbito das universidades e demais instituições de pesquisas que surgem descobertas, formulações de tratamentos e/ou táticas de combate e outras ações fundamentais em nome da saúde coletiva. Além de importante na vigilância e tratamento das doenças, o saber médico científico é diretamente afetado pelo comportamento e consequências das arboviroses. A ausência de vacina, a dificuldade de exterminar o mosquito vetor e outros empecilhos se caracterizam como desafios à medicina e à saúde pública. No caso da tríade aqui preconizada, o problema se torna ainda maior, uma vez que boa parte dos sintomas é comum às três infecções,

ocasionando a dificuldade de diagnóstico. As pessoas assintomáticas ou as que por diferentes razões não procuram atendimento especializado são outro agravante às estatísticas e planos de estratégias. Devemos citar, ainda, a situação social das diferentes regiões afetadas. A falta de saneamento, nutrição e orientação higiênica representam a realidade de vários grupos sociais, tornando mais grave o panorama da existência de criadouros do *Aedes Aegypti*.

Tomando novamente a *Dengue* como exemplo, Shepard *et al.* (2011 *apud* TEICH *et al.*, 2017:268) definem que “o custo associado ao manejo da dengue no Brasil é considerado o maior das Américas, correspondendo a 42% dos gastos totais relacionados à doença no continente”. Os gastos previstos em leis orçamentárias anuais para a saúde<sup>9</sup> (de 2015 a 2020) mencionam como principais subáreas: assistência hospitalar e ambulatorial, atenção básica, suporte profilático e terapêutico, administração geral, vigilância epidemiológica e “outros”. Nos cabe destacar que muitas vezes os recursos previamente definidos necessitam de crédito suplementar, sobretudo na ocorrência de epidemias, e por vezes são insuficientes quando distribuídos entre os estados, municípios e Distrito Federal. O aspecto econômico do impacto da tríade deve considerar, juntamente, os prejuízos às empresas, a partir da impossibilidade de realização do trabalho que as arboviroses ocasionam em funcionários infectados, bem como os malefícios a diversos ramos comerciais, afetados pela ausência temporária de clientes debilitados.

No início deste ensaio, mencionamos um decreto e sua revogação acerca de portas de entrada para futura privatização do Sistema Único de Saúde. Boa parte dos debates, principalmente os veiculados em canais virtuais como as redes sociais, enfatizavam a importância do SUS. Tema recorrente nessas discussões era o de que as responsabilidades do sistema ultrapassavam o atendimento às doenças e incluíam, também, ações de prevenção, vigilância sanitária e uma série de outras necessidades da convivência populacional<sup>10</sup>.

Com base nas práticas de enfrentamento e manejo das arboviroses, nos juntamos a esforços de conscientização e afirmamos que a operacionalização de um SUS ultrapassa o atendimento hospitalar. Ele está inevitavelmente correlacionado às ações dos órgãos de administração da saúde pública no Brasil. Órgãos gestores, com ênfase no Ministério da Saúde, mantém parcerias para campanhas de prevenção,

como a manutenção de agentes comunitários de saúde para orientação à população e feitura de estatísticas sobre a presença de mosquitos ou larvas, a circulação de propagandas na TV aberta, a disponibilização de comitês e ouvidorias de comunicação com a sociedade e outras. Todas custam dinheiro, que vem de diferentes fontes de receita (como a arrecadação de impostos pagos pela população, inclusive no preço de produtos e serviços como IPVA<sup>11</sup> e IPTU, da contribuição previdenciária arrecadada pelo âmbito federal, etc.). É pensando em ações que evitem a sobrecarga e permitam a manutenção do SUS que as atividades de prevenção e combate ao *Aedes Aegypti* ocorrem. A maioria das unidades básicas de saúde e hospitais brasileiros, por exemplo, possuem profissionais e equipamentos preparados para identificar possíveis casos de infecção pelo mosquito vetor, mesmo que dificuldades em diagnosticar a presença de uma arbovirose ou mesmo em distinguir qual dos três arbovírus afetam um paciente ainda apareça algumas vezes. Essa preparação foi possível graças a mobilização orçamentária e comunicativa de instâncias públicas, a exemplo da Universidade Aberta do SUS, criada em 2010 pelo Ministério da Saúde, que moveram esforços em nome da informação, prevenção e combate ao vetor, ofertando cursos de manejo para profissionais da saúde, sendo alguns também abertos à comunidade. Esta e todas as demais atitudes envolvem planejamento financeiro. Um dos desafios enfrentados pelos órgãos gestores do SUS é o de mantê-lo financeiramente. A já mencionada escassez de profissionais e equipamentos suficientes, bem como sucateamento ou ausência de unidades de saúde em certas localidades, experencia um espaço que demonstra que é preciso uma reformulação orçamentária para melhorias do sistema público de saúde.

A ideia de prevenção, que deve ocorrer em rede, sobretudo no caso das arboviroses que são transmitidas por um mosquito que se locomove e se reproduz em diversas habitações humanas, é fundamental para compreendermos a valorização da saúde como pauta imprescindível para a boa imagem de um governo, para o bom comércio, para a operacionalização de direitos sociais, em resumo para o funcionamento social desejado. A ocorrência de arboviroses evidencia, também, outras questões, a exemplo de disparidades regionais em termos de saneamento básico e atendimento hospitalar gratuito disponível.

Ao consultar portais virtuais como o Sistema de Cadastro e Consulta de Legislações do SUS, disponíveis na internet para consulta aberta, é possível encontrar principais portarias, por vezes igualmente

<sup>9</sup> Cifras detalhadas sobre os gastos governamentais com as arboviroses para cada ano podem ser encontradas em boletins de transparência pública disponibilizados por órgãos governamentais da saúde.

<sup>10</sup> É importante informar que considerável parcela da sociedade brasileira desconhece todas as atribuições do SUS, bem como as legislações que o regem.

<sup>11</sup> IPVA- Imposto sobre a Propriedade de Veículos Automotores; IPTU – Imposto Predial e Territorial Urbano.



publicadas no Diário Oficial da União, acerca de orçamentos e outras instruções do Governo Federal sobre o Sistema. É importante destacar que, do ponto de vista da metodologia da história, deve-se pensar nas possibilidades, mas também nos limites de aplicação dos dispositivos legais. Exemplo da disparidade entre textos de lei e projetos de prevenção e sua aplicação prática encontra-se na falta de saneamento em algumas regiões, onde acumula-se lixo e recipientes com água parada. Por vezes os planejamentos de prevenção não alcançam essas localidades, por diferentes motivos- ausência de orientação ou descaso da população para o combate aos criadouros do mosquito, negligência dos governos estadual, municipal ou federal, etc.

A distribuição habitual de recursos financeiros federais para a vigilância em saúde se dá por algumas definições principais, a saber, as portarias anuais que indicam o Piso Fixo de Vigilância em Saúde (PFVS) e o Piso Variável de Vigilância em Saúde (PVVS). A verba fixa é contabilizada segundo a situação epidemiológica de cada estado e município. A verba variável é calculada a partir da adesão das unidades da federação a programas de prevenção, vigilância e qualificação de pessoal oferecidos periodicamente pelo Ministério da Saúde. Conforme apontam Vanessa Teich *et al.* (2017), existem, ainda, assistências financeiras complementares e casos de repasses mensais “para o fortalecimento do combate a endemias”.

Se no tópico anterior expusemos boletins referentes ao período de 2015-2020, para evidenciar como as arboviroses aparecem como grave problema social enfrentado pelo SUS todos os anos, neste nos limitaremos a fornecer levantamentos contábeis apenas de alguns períodos. A ideia é demonstrar a rede que o SUS envolve.

Vanessa Teich *et al.* (2017), analisam o impacto econômico das arboviroses no Brasil para o ano de 2016. Além de apontarem valiosas informações, a exemplo de que o ambiente no país é deveras propício para a permanência e disseminação do *Aedes Aegypti* e que a propagação do vetor tem negativos impactos clínicos e econômicos, os autores fornecem estatísticas de gastos contra as três arboviroses que aqui estudamos. Após uma análise detida dos boletins epidemiológicos e portarias do Governo Federal para a Saúde, apresentam:

(...) O investimento para combate ao vetor foi de R\$ 1,5 bilhão no Brasil e o custo reportado pelo governo federal para aquisição de inseticidas e larvicidas foi de R\$ 78,6 milhões (...) Custos totais com o manejo das arboviroses atingiram impacto de R\$ 2,3 bilhões no Brasil, em 2016. Minas Gerais, São Paulo, Bahia e Rio de Janeiro apresentaram os maiores custos. (...) Arboviroses geram consideráveis impactos econômico e social ao Brasil. Custos de combate ao vetor, custos médicos diretos e

custos indiretos representaram 2% do orçamento previsto para a saúde no País, em 2016. (TEICH *et al.*, 2017:267)

Nordeste e Sudeste encabeçaram os maiores custos. O valor de 2% é significativo quando comparado ao orçamento total. Os gastos com larvicidas e inseticidas demonstram mais uma tarefa realizada pelo SUS, reforçando o argumento de que sua alçada ultrapassa o âmbito do atendimento hospitalar. A existência de custos médicos diretos – voltados ao atendimento do paciente infectado -, e dos custos indiretos – os que vão além dos primeiros e estão relacionados a consequências como perda de produtividade, grande número de mortes precoces de pacientes e outros-, corrobora com a ideia de interligação entre orçamento federal, funcionamento social e a saúde pública.

Em 2017, a Secretaria de Vigilância em Saúde do Ministério da Saúde, lançou a publicação “Vírus Zika no Brasil: a resposta do SUS”, que “mostra o esforço de cientistas, servidores públicos, profissionais de saúde e dos profissionais de comunicação em oferecer respostas à sociedade” (MS, 2017). O texto de 137 páginas fornece um histórico da chegada do *Zika* em formato epidêmico no Brasil e respostas oferecidas pela rede da saúde pública na qual o SUS está inserido. Surpresas, confusões e incertezas sobre diagnósticos, desafios aos profissionais e à população, importância e obstáculos à vigilância e à comunicação, construção de estratégias, parcerias na investigação científica sobre a moléstia, ações de enfrentamento da epidemia e disseminação do conhecimento são alguns dos principais tópicos. Muitos são os pontos que evidenciam a urgência da saúde pública como rede de preocupação coletiva neste documento. Aqui, enfatizaremos um apontamento encontrado na página 22, que afirma que quando os órgãos gestores da saúde decretaram o contexto emergencial da doença- e maior parte desta descoberta fora possível pelo grande número de casos de bebês com microcefalia atendidos em hospitais do SUS-, Dilma Rousseff, presidenta do Brasil na época, “deixou em segundo plano a crise política que o governo vivia (...)”.

Iniciara-se um contexto de ações de premência para combate à enfermidade, com “mobilização política e institucional de grande envergadura, iniciada em novembro de 2015, quando ainda eram enormes as lacunas de informação e as incertezas sobre a natureza da epidemia” (MS, 2017:22). O histórico deixa claro como a epidemia de *Zika* era um problema de todos- sociedade, órgãos de saúde, governo. É indispensável ressaltar a importância do SUS no âmbito de tratamento e combate à epidemia, desde a preparação de profissionais da saúde para manejo dos pacientes infectados, até campanhas de prevenção veiculadas em diversos meios de comunicação. Notemos ainda que sem os registros de casos atendidos pelos estabelecimentos do SUS talvez a identificação da



moléstia demorasse mais ainda, piorando o contexto caótico. O acesso público a serviços de saúde propiciados pelo mesmo sistema foram cruciais no atendimento de orientação dos afetados pelo vírus e suas famílias.

Já dissemos que o SUS envolve diferentes instâncias gestoras e é uma das principais ferramentas de bem-estar social a partir do acesso gratuito à saúde que é, de igual forma, uma maneira de combater desigualdades sociais. Além dos órgãos gestores, outras parcelas sociais, como profissionais da saúde, população e outras instâncias de governo também fazem parte da rede. Contudo, essa correlação entre várias partes envolvidas, que é inevitável, também tem pontos falhos. A ligação nem sempre é harmoniosa e de negociação. Diversos conflitos permeiam a existência do acesso gratuito à saúde: falta de realização perfeita de convênios entre o SUS e a rede privada quando esta aparece como complementar ao serviço público, disputas político-partidárias que por vezes afetam negativamente o orçamento destinado pelo Governo Federal ao Sistema Único de Saúde, falta de recursos materiais e humanos, más gestões das unidades de saúde, ocorrência de surtos epidêmicos que atingem proporções não esperadas, corrupção e desvio de verbas, entre outros. Os fatores mencionados, que fazem parte do espaço de experiência da rede do qual o SUS faz parte, demonstram um horizonte de expectativa em grande parte incerto. As estatísticas das arboviroses, sobretudo quando somadas a problemas nas ações de prevenção devido a fatores como ausência de saneamento básico, nos fazem crer que o *Aedes Aegypti* infectado será um inimigo ainda presente por muito tempo, se tornando elemento fundamental das projeções para o horizonte de expectativa da saúde no Brasil. Por esta e por outras razões- as doenças congênitas, as doenças adquiridas, as doenças ascendentes, as doenças inesperadas, as vigilâncias epidemiológicas, sanitárias e outras exigências biológico-sociais, a manutenção e melhoramento do SUS precisa fazer parte tanto do espaço de experiência, quanto do horizonte de expectativa, de forma mais concreta e apoiada pelas instâncias de poder e demais segmentos da sociedade.

#### d) *Alguns versos finais*

O Sistema Único de Saúde abrange a grade de hospitais públicos, mas também é mais do que ela. Acompanha o movimento vital da população, do ponto de vista bio-patológico, do político, do econômico, do sociocultural. O caso das arboviroses e as respostas do SUS demonstram-no como instrumento indispensável na prevenção e combate às moléstias. Aqui focamos em três, das quatro principais arboviroses urbanas transmitidas pelo *Aedes Aegypti*, mas devemos recordar que além delas, o SUS é responsável por

cuidados a vários outros setores de saúde com acesso gratuito.

Um dos pontos-chaves de nosso texto evidenciou a fundamentalidade da noção de saúde em rede, com órgãos governamentais, instituições de pesquisa e população inevitavelmente correlacionados na análise da importância do SUS e a ocorrência de arboviroses. No cerne da ideia de saúde em rede está a de prevenção em rede, mais um dos trabalhos do SUS que envolve a cooperação das demais instâncias sociais. Nosso espaço de experiência evidencia algumas insuficiências e incertezas, como as falhas orçamentárias e constantes ameaças, a exemplo do decreto que citamos na primeira parte deste ensaio. Para a concretização da prevenção em rede (das arboviroses e também de outras moléstias), a educação preventiva precisa estar em nosso espaço de experiência para auxiliar num horizonte possível de boas expectativas quanto à saúde pública e manutenção do Sistema Único, pois é uma das maneiras de evitar a proliferação do mosquito e outros agentes causadores de doenças.

Outro desafio ao SUS é a convivência com a rede privada. Ao mesmo tempo em que a concomitância dos dois sistemas pode ser benéfica no que tange ao “desafogamento” de leitos e profissionais, os conflitos existem, sobretudo quando tomamos o sistema privado como um mercado que compete com o sistema público. Recentemente a Agência Nacional de Vigilância Sanitária (ANVISA) do Brasil divulgou a nota técnica n. 49/2020, que versa sobre “orientações para monitoramento de eventos adversos pós-vacinação” em clínicas privadas, reconhecendo que na atual vigência da pandemia de coronavírus SARS-CoV-2, estas teriam papel fundamental no monitoramento dos efeitos da futura vacina, contanto que seguissem as orientações propostas pelo documento. Uma das principais diretrizes se referia à necessidade de notificação dos casos adversos provocados pela vacina. A ANVISA determina padrões tanto para a rede pública, quanto para a privada. A nota técnica da agência de vigilância sanitária é exemplo da necessidade de cooperação entre as duas redes, apontando para a importância do trabalho conjunto-envio de informações de casos adversos tanto nos hospitais públicos quanto nos particulares- em nome do aumento da eficiência do combate à pandemia que afeta a todos, sobretudo por sua grande capacidade de contágio.

Ainda sobre o binômio rede particular e rede pública, a nota técnica foi lançada ao mesmo tempo em que uma enxurrada de debates acontecia nas diferentes mídias. O cerne desses debates, que ensejaram e ensejam questionamentos inevitavelmente correlacionados, que envolvem inclusive as disputas político-partidárias, era a discussão da possibilidade de a rede privada de saúde monopolizar ou ao menos ter

prioridade de compra e distribuição de vacinas. Para a parte defensora da ideia, essa seria a solução para entraves burocráticos e financeiros pelos órgãos relacionados à gestão do SUS. O problema da falta de seringas, que também apareceu como parte do desafio contra a COVID-19 no Brasil foi, por vezes, tomado como argumento. Para a parte que vai contra a ideia, o monopólio contribuiria ainda mais ao panorama de desigualdades de acesso à saúde, refletido da situação social daqueles que não têm acesso à saúde privada. Além disso, a vantagem concedida à rede privada ameaçaria o compromisso do Governo do Brasil com a garantia do acesso gratuito à saúde. O atual espaço de experiência da saúde no Brasil evidencia os prejuízos de uma possível vantagem ou monopólio pela rede privada. Ainda que com imensas falhas em implementar vários de seus princípios fundamentais como previstos pela Carta Magna de 1988, o SUS atende a mais de 70% da população (IBGE, 2020), sendo parte desta cifra formada por tratamentos contínuos, incluindo a distribuição gratuita de remédios para doenças crônicas como a diabetes, ofertados a pessoas que não possuem condição de pagar pelos serviços médicos privados.

A pandemia de COVID-19 tem se demonstrado grave problema mundial atual. No Brasil, o número de mortes entre a ascensão em 2020 e a primeira semana de janeiro de 2021 ultrapassou a quantia de 200 mil óbitos. Tanto o manejo dos casos, quanto os debates sobre o tratamento têm representado gigantesco desafio à gestão e operacionalização do SUS. A falta de certezas sobre o comportamento do vírus, a inexistência de um tratamento totalmente eficaz comprovado e o potencial de ceifar vidas de pacientes e de profissionais da saúde que trabalham no combate à enfermidade, são algumas das principais facetas deste problema que é, principalmente, do Sistema Único de Saúde. No início de janeiro de 2021, após um longo período de trabalho investigativo colaborativo, o Instituto Butantan anunciou grande percentual de eficácia em casos graves e contra mortes, da vacina *Coronovac*, desenvolvida por seus pesquisadores em parceria com a empresa farmacêutica chinesa Sinovac. Em seguida, o Ministério da Saúde firmou contrato para comprar doses em larga escala da vacina. Em meados do mesmo mês, Mônica Calazans, uma enfermeira de 54 anos, era a primeira vacinada do país, pelo Sistema Único de Saúde. A disponibilização da vacina à população pelo SUS começou a ocorrer com a vacinação de grupos prioritários (profissionais da saúde, idosos e outros). Prossegue de forma gradual. Outras vacinas têm sido estudadas também. Em meio às dificuldades contextuais, obtivemos, com a *Coronovac*, uma significativa conquista obtida pelo trabalho dos diversos pesquisadores e pesquisadoras envolvidos.

O debate sobre possíveis vacinas merece especial atenção, visto que envolve uma série de outras questões, a exemplo de atitudes xenofóbicas e ideológicas quanto a aceitação da importação de vacinas produzidas em países do oriente. Outro exemplo é encontrado na própria recusa de algumas pessoas quanto às medidas de prevenção e luta contra o Coronavírus. O movimento antivacina, que se popularizou na internet ganhando grande número de adeptos, se caracteriza como grave entrave nas ações de combate, uma vez que, ainda que não se saiba com precisão o comportamento do vírus, sabe-se que ele se propaga com grande facilidade e pessoas infectadas que não seguem protocolos, como o uso de máscaras e isolamento social, podem ser responsáveis por infectar outras que seguem tais regras. Movimentos que se opõem à vacina e são deveras prejudiciais aos esforços do SUS e da população, falta de conhecimento quanto às ações do Sistema, seus órgãos gestores e instituições de pesquisa (sobretudo as universidades, institutos e fundações) a nível nacional e internacional, a propagação de *Fake News* e a crença indubitável em remédios milagrosos que protegem completamente a imunidade, são alguns outros empecilhos ao melhoramento da saúde pública e da rede de atendimento do Sistema Único de Saúde na pandemia de COVID-19.

Todos esses problemas se agravam pela ocorrência paralela de outras doenças, dentre as quais se incluem a tríade de arboviroses urbanas, com ênfase na *Dengue*, que entre 2019 e 2020 apresentou expressivo número de casos no Brasil. Como não se sabe ao certo sobre uma grade de sintomas específicos à COVID-19, que não apareçam em outras doenças também, a confusão de diagnósticos pelos sintomas da citada arbovirose e do Corona vírus pode se apresentar como outra dificuldade possível à atuação do SUS.

Esperamos que este ensaio, que é uma análise histórica a partir do conceito central de correlação inevitável, e que também aplica a um caso específico duas das principais noções históricas propostas por Reinhart Koselleck (2006), seja, de igual modo, um alerta sobre como nosso espaço de experiência evidencia que precisamos reverter um horizonte de expectativa que aponta para o possível desmonte de um dos principais direitos garantidos pela Constituição Federal de 1988: o acesso gratuito à saúde pelo SUS.

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## Environmental Exposure to Glyphosate and Risk of Asthma in an Ecological Study

By Medardo Avila-Vazquez, Flavia Silvina Difilippo, Bryan Mac Lean  
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**Abstract-** There is strong evidence of the link between asthma and occupational exposure to pesticides and even glyphosate in agricultural workers, but it is limited on asthma and environmental or residential exposure to these chemicals. This research analyzes the prevalence of asthma in an agricultural town with high use of pesticides, mainly glyphosate. Is an ecological study conducted in Monte Maíz, Argentina, composed of a chemical and environmental analysis to determine the burden of exposure to glyphosate and pesticides in general, and a cross-sectional asthma study that uses the methodological criteria of the International Study of Asthma and Allergies in Childhood (ISAAC); the prevalence's found in Monte Maíz are compared with the results of ISAAC in Argentine cities with low exposure to pesticides. In Monte Maíz area 975 tons of pesticides are sprayed (650 are glyphosate) that are also stored inside the town.

**Keywords:** *asthma, environmental exposure, pesticides, glyphosate, environmental health.*

**GJMR-F Classification:** *NLMC Code: WF 140*



*Strictly as per the compliance and regulations of:*



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# Environmental Exposure to Glyphosate and Risk of Asthma in an Ecological Study

## Environmental Exposure to Glyphosate and Asthma

Medardo Avila-Vazquez <sup>α</sup>, Flavia Silvina Difilippo <sup>ο</sup>, Bryan Mac Lean <sup>ρ</sup> & Eduardo Maturano <sup>ω</sup>

### Highlights

- \* Ecological study evaluating pesticide contamination in an Argentine farming town and measuring asthma prevalence
- \* Determination of pesticide exposure burden and presence of pesticides in environmental matrices. Asthma prevalence was measured with the same technique that the International Study on Asthma and Allergic Diseases in Children (ISAAC) assess asthma in Argentine cities.

**Results** detect high contamination and environmental exposure to glyphosate, a herbicide that prevails over all other pesticides

- \* The asthma prevalence is increased in all age groups,
- \* In children aged 6-7 years it is 52.4% and in children aged 13-14 years it is 39.9% while the national prevalence is 13.6% for ISAAC in Argentina
- \* In children 13-14 years old exposed to glyphosate in this farmer town the asthma risk is OR: 4.64 (CI: 3, 26 - 6.60).

### Environmental exposure to glyphosate and risk of asthma

Asthma cases distribution and their relationship with environmental pollutants in the agricultural town of Argentina



### Results

higher prevalence near grain silos compared to other sectors of the town, OR: 1.43 (CI: 1.18 - 1.72) in children 13-14 years old.

With respect to cities not exposed to glyphosate, the risk of asthma is OR: 4.64 (CI: 3.26 - 6.60)

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**Abstracts-** There is strong evidence of the link between asthma and occupational exposure to pesticides and even glyphosate in agricultural workers, but it is limited on asthma and environmental or residential exposure to these chemicals. This research analyzes the prevalence of asthma in an agricultural town with high use of pesticides, mainly glyphosate. Is an ecological study conducted in Monte Maíz, Argentina, composed of a chemical and environmental analysis to determine the burden of exposure to glyphosate and pesticides in general, and a cross-sectional asthma study that uses the methodological criteria of the International Study of Asthma and Allergies in Childhood (ISAAC); the prevalence's found in Monte Maíz are compared with the results of ISAAC in Argentine cities with low exposure to pesticides. In Monte Maíz area 975 tons of pesticides are sprayed (650 are glyphosate) that are also stored inside the town. High and preponderant levels of glyphosate were found in the soil and in corn husk and soybean powder. The environmental exposure burden to pesticides was 121 kilos, for glyphosate 81 kilos per person per year, while this burden in the entire country is 7.9 and 6 kilos respectively. The prevalences of asthma found were several times higher than those of reference in all ages, the risk of asthma in children of 13 and 14 years old, with respect to those of three large Argentine cities, refers to an OR of 4.64 (CI: 3, 26 - 6.60). These results highlight a relationship between environmental and residential exposure to pesticide, glyphosate predominantly and high prevalence of asthma, while experimental studies support the biological plausibility of this association.

**Keywords:** *asthma, environmental exposure, pesticides, glyphosate, environmental health.*

## I. INTRODUCTION

Asthma is the most commonly occurring chronic childhood disease in the world (1,2). According to the Global Asthma Report 2014 (GAR 2014), 14% of the world's children and 8.6% of young adults experience asthma (3). Childhood asthma is particularly prevalent in Latin America, and the International Study on Asthma and Allergic Diseases in Children (ISAAC) has identified environmental contamination as a key factor in the region's elevated rates of the disease (1). The International Study of Asthma and Allergies in Childhood (ISAAC) surveyed a representative sample of 798,685 adolescents aged 13-14 years in 233 centres in 97 countries between 2000 and 2003. In ISAAC these adolescents were asked whether they had experienced wheeze, a symptom that is commonly attributable to asthma or use of bronchodilator aerosols.

Globally, too, exposure to environmental toxins explains the rise in asthma rates (4,5). Epidemiological studies reveal an association between pesticide exposure and increased prevalence of asthmas, while experimental testing has shown that certain pesticides generate immunological imbalances characteristic of asthma, fortifying the link between occupational exposure to pesticides and asthma, especially in farmers (6,7). However, there is a gap in knowledge with

respect to asthma and residential environmental exposure to pesticides, especially glyphosate.

In Argentina, asthma is a serious health problem, causing more than 400 deaths and 15,000 hospitalizations annually (8,9). As elsewhere in South America, rates of pesticide application have increased dramatically in Argentina with the expansion of transgenic crops since the mid 1990s (10,11).

Transgenic crops now cover an area of 25 million hectares in Argentina. In 2013, 318,000 tons of pesticides were applied within the country's borders, including 250,000 tons of glyphosate (11). Most of these pesticides were applied in a region where about 12 million people reside. Concurrent with these changes, doctors in the region report a shift in the morbidity and mortality profile of rural populations (12). Along with other conditions, wheezing and asthma are now frequently detected.

Monte Maíz (Province of Córdoba) is a town located in the heart of Argentina's main agricultural region where inhabitants have expressed concern about an apparent increase in diseases that were previously perceived as infrequent. A group of neighbors headed by their Mayor requested an evaluation of the health status of their local population from a research team at the Division of Medical Sciences of the National University of Córdoba (UNC).

In this context, a study was carried out in order to determine if there had been an increase in the prevalence of cancers, reproductive, endocrine and immunological problems, and asthma linked to a greater burden of exposure to pesticides. The objective was to analyze the environmental exposure to pesticides as a risk factor for the above-mentioned pathologies (and determine if any particular pesticide is preponderant), and to correlate environmental factors in order to develop a causality hypothesis. The results of the analysis of cancer and reproductive disorders have already been published (13,14), while those of asthma provide the basis for this article.

## II. MATERIAL AND METHODS

This ecological study was designed to test for possible correlation between residential exposure to pesticides and the prevalence of asthma in Monte Maíz by comparing local rates of disease with those measured by ISAAC in Argentine cities with low or no residential exposure to pesticides. The study comprises both an analysis of chemicals in the environment, and a cross-sectional study of asthma prevalence. The latter was carried out via the administration of a populational survey designed to georeference each datum acquired utilizing census radii from the National Census Institute (map in Figure 1).





**Figure 1:** Figura 1 Map of Monte Maíz census radii by National Institute Census divide the town in nine sectors outweighed demographically.

The presence or absence of asthma was recorded not according to existing medical diagnosis, but rather in accordance with ISAAC's previously validated survey instrument (15). ISAAC's questionnaire is based on questions such as whether the respondent experienced wheezing in the last year, or use of bronchodilator aerosols. This study's implementation of ISAAC's survey instrument facilitates comparison between the data generated elsewhere by ISAAC and the data generated in Monte Maíz.

The environmental analysis reviewed and georeferenced garbage dumps, industrial sites, grain stockpiles, and pesticide deposits in each census radius. Through the synthesis of information acquired from interviews with key informants (agronomists, farmers and pesticide applicators), pesticide application rates were determined to calculate the burden of exposure.

The burden of exposure was then verified by measuring quantities of the most commonly used pesticides in soil and volatile grain dust (from pulverized grain husk). Sampling was carried out by researchers from the Center for Environmental Research at the National University of La Plata. Pretreatment and analysis of the samples were carried out in accordance with international regulations using mass spectrometry and liquid chromatography (16, 17).

The study area was Monte Maíz, a town of 7,788 inhabitants, located at 33°12'south latitude and 62°36' west longitude. The study population comprised all inhabitants of Monte Maíz, with a special focus on children 6 and 7 years old, and 13 and 14 years old from across the entire town. Children from these age groups were analyzed against the control population: children from those same age groups who live in three large Argentine cities (Buenos Aires, Rosario and Córdoba), who were evaluated by ISAAC. The data from this study has also been evaluated against the data on asthma prevalence reported by the Argentine Society of Pediatrics and Ministry of Health of the Nation (9).

In the statistical analysis, asthma was the dependent variable. The independent variables were sex, age, occupation, time living in the area of study, smoking, premature birth, radius of residence within the town, and education. Asthma prevalence rates were generated by age groups. To investigate the relationship between the variables, a multivariate study was carried out using principal component analysis. The association between asthma and independent variables was analyzed by Pearson's bivariate correlation. Contingency tables were created to measure the levels of risk in the most significant correlations, both with a 95% confidence interval. The INFOSTAT (UNC), SPSS and EPIDAT (PAHO) programs were used. Environmental and asthma maps were constructed using the Quantum GIS 2.4 program.

This study was conducted in accordance with the Declaration of Helsinki and Law No. 9694 of the Province of Córdoba, which regulates human health research (19). The health surveys were carried out by students and professors of the UNC's medical program, and the environmental analysis was carried out by members of the School of Geography. All the teams worked simultaneously and the fieldwork was completed in October 2014.

### III. RESULTS

#### a) Epidemiological Study

Every home in the town was visited by the survey teams. In some homes there was no one to answer and in 4.8% the inhabitants declined to respond to the survey. Data were collected from 4,959 people,

some 62% of the population. Demographic composition is represented in table 1.

The general asthma rate of the population was 16.2%. Among them 22% were smokers and 4.3% reported a history of neonatal prematurity. The prevalence in the 18 to 40 year-old group was 12.6%, higher than that of the entire country (5.9%) according to the National Asthma Prevalence Survey of 2015 (19), with an OR: 2.32 (CI: 1.79 – 3.01). In children aged 13 and 14, the prevalence was 39.9%, while in those aged 6-7 years it reached 52.4%. In three large Argentine cities, ISAAC detected a prevalence of asthma of 13.6% among children aged 13-14 (20). In Monte Maíz, children of the same age group had a prevalence of 39.9%, with an OR of 4.64 (CI: 3.26-6.60).

*Table 1:* Monte Maíz Population surveyed: Characteristics, absolute numbers and percentages

Characteristics	Magnitude
Number of individuals recorded	4,959 (61.98%)
Male	2361 (47.61%)
Female	2597 (52.37%)
Average age of Population	36.03 years
People 0-15 years	1175 (23.69%)
People ≥16 years with complete primary education	3313/3744 (88.49%)
People with health insurance	3859 (78.01%)
Percentage of people with ≥5 years residence time	4141/4328 (95.68%)
Families of rural workers, farmers and agronomists	270 families, 970 persons
Smokers	793/3780 (20.98%)

The principal components analysis positively linked asthma with children, negatively with smokers, and found no association with any particular occupations. In Pearson's Bivariate Correlations there was a positive spatial relationship with the inhabitants of radii 16 and 17, but it had no bilateral significance with people with direct participation in agricultural activity (significance value: 0.295).

The probability of suffering asthma was higher (OR: 1.43 [CI: 1.18 - 1.72] for residents living near grain storage sites in the south-southwest direction in radii 16 and 17. The asthma prevalence rate in children 6-7 and 13-14 years-old in those sectors were 53.3% and 42.8% respectively, the highest among all the radii of the town.

#### b) Environmental analysis

The population of this region is concentrated in the town of Monte Maíz, which has quality drinking water and an adequate sewer network. Urban solid waste is accumulated in an open-air dump located 800 meters from the town, in which no occurrences of fire or combustion have been reported for more than five years. To the south of the town there are two metallurgical factories which produce agricultural equipment and use methane gas as fuel. Forests or grasslands on the periphery of the town have been

replaced by crops. These crop fields, which are in many cases adjacent to homes, receive systematic applications of pesticides.

The agricultural area of Monte Maíz comprises 65,000 hectares. Of these, 45,000 hectares are planted with transgenic soybeans and 20,000 hectares with transgenic corn (both glyphosate resistant). In the winter season, 15,000 hectares of wheat are sown. Agronomists and pesticide applicators interviewed report that soybean and corn crops consumed 10 kg of glyphosate and 5 kg of additional pesticides (including atrazine, 2-4D, chlorpyrifos, endosulfan, cypermethrin, and epoxiconazole) per hectare per year. As a whole, the area of study consumes 975,000 kg of pesticides annually, of which 650,000 kg are glyphosate. This constitutes a general environmental burden of pesticide exposure of 121 kg per person per year, and of glyphosate in particular of 81 kg per person per year. This environmental burden varies depending on individuals' occupational or residential proximity to agricultural activity. The national pesticide exposure burden is 7.9 kg per person per year, and 6 kg of glyphosate per year (see table 2).



Table nº 2

Pesticide and glyphosate utilization rates in Monte Maíz, hectares cultivated per year and residential pesticide and glyphosate exposure burden per person per year

<b>Pesticides utilization rates (everything)</b>	<b>15 kilos / ha/ year</b>
<b>glyphosate utilization rates</b>	<b>10 kilos/ha/year</b>
<b>glyphosate resistant cultivated hectares</b>	<b>65.000 hectares</b>
<b>Total pesticides used per year</b>	<b>975.000 kilos</b>
<b>Total glyphosate used per year</b>	<b>650.000 kilos</b>
<b>Pesticide burden in Monte Maíz</b>	<b>121 kilos /inhabitants /year</b>
<b>Glyphosate burden in Monte Maíz</b>	<b>81 kilos /inhabitants/year</b>
<b>Total pesticides Argentina 2013</b>	<b>371.000.000 kilos</b>
<b>Total glyphosate in Argentina 2013</b>	<b>240.000.000 kilos</b>
<b>Pesticide burden in Argentina 2013</b>	<b>7,9 kilos por persona</b>
<b>Glyphosate burden in Argentina 2013</b>	<b>6 kilos por persona</b>

In Monte Maíz there are huge silos and grain stores which release pulverized soy and corn into the air. A predominantly northeast to southwest bearing wind carries the dust towards radii 16 and 17 (see location in Figure 2). Chemical analyses confirmed the high exposure estimated based on interview data. Glyphosate and ácido aminometilfosfónico (AMPA, its

metabolite) were detected in 100% of the soil and dust samples. Glyphosate and AMPA concentrations exceeded concentrations of other pesticides in all samples, averaging concentrations of 505 and 607 ppb, respectively, followed by chlorpyrifos (14 ppb) and epoxiconazole (2.3 ppb) (see table 3).

Table 3: Measurements pesticides in environmental matrices, main findings

S: Site sampling	Glifosato	AMPA	2,4 D	Atrazina	Clorpirifos	Endosulfan I	Endosulfan II	Cipermetrina	Epoxiconazol
S1 drinking water network	< 2 ppb	< 2 ppb	< 1 ppb	< 0.5 ppb	DNC	DNC	DNC	<0.005 ppb	<0.005 ppb
S5 crop field soil	41 ppb	116 ppb	< 5 ppb	6.4 ppb	242 ppb	< 1,5 ppb	2.2 ppb	58 ppb	3 ppb
S6 children's playground soil	2792 ppb	797 ppb	S/D	S/D	4.4 ppb	< 1,5 ppb	< 1,5 ppb	4 ppb	3.4 ppb
S6 children's playground grain husks from silos	505 ppb	607 ppb	S/D	S/D	14 ppb	DNC	< 1,5 ppb	DNC	2.3 ppb
S8 pesticides deposits soil	3868 ppb	3192 ppb	128 ppb	52.5 ppb	150.4 ppb	17.5 ppb	338 ppb	180 ppb	6.3 ppb

Reference S located sampling site (S 5, S6 and S8) in map of Figure 3. DNC: Detectable no quantifiable.

Center for Environmental Research, Faculty of Exact Sciences of National University of La Plata.

The samples of the site square no. 6 (see map figure 2) contain 68 times more glyphosate than the soil of a cornfield of site no. 5. Samples from site No. 8, taken from the soil of the pedestrian path of a pesticide deposit, is where the highest concentrations of all pesticides were detected. As elsewhere, concentrations

of glyphosate (3868 ppb) and AMPA (3192 ppb) far exceed concentrations of other pesticides, such as endosulfan II (338 ppb), and chlorpyrifos (242 ppb) (see in table 3).

## Map 2: Monte Maiz Environmental Factors Pollution

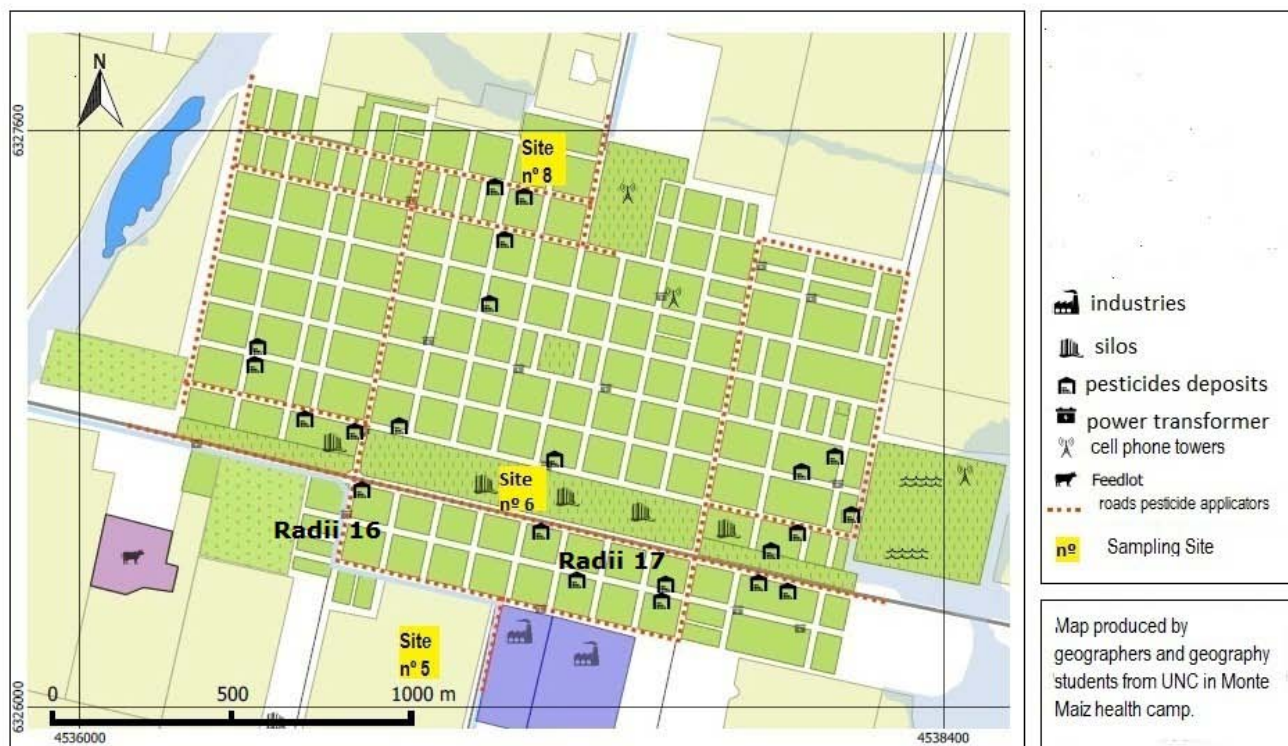


Figure 2: Figure 2 Map of environmental factors pollution on Monte Maíz and main sampling site

### IV. DISCUSSION

In Monte Maíz, industrial pollution is minimal, there has been no combustion of waste in the landfill in the last 5 years, and a good standard of living prevails. However, with the proliferation of transgenic crop production since the mid 1990s, pesticide deposits have multiplied in the area, now numbering twenty-two.

At least 975,000 kilos of pesticides per year are applied in fields surrounding Monte Maíz, and concentrations found inside the town were several times higher than in the cultivated fields (see table 3), reflecting the fact that the town is the operational base for pesticide applications in the region.

We detected glyphosate in 100% of grain dust samples and its concentration was 20 times higher than other pesticides. Glyphosate was always found

coexisting with other pesticides, revealing that its presence is not due to use in gardening.

Contamination with glyphosate in particular and with pesticides in general is predominant in this environment. The burden of residential exposure to glyphosate is 13.5 times greater than the average burden of the national population, and within the town this burden seems to be even greater in radii 16 and 17 where the grain dust impregnated with glyphosate is carried by the wind.

In GAR 2014, the global prevalence of asthma for people 18-45 years-old is recorded at 8.6%, placing Argentina slightly below average (3). However, 18-45 year-old residents of Monte Maíz experience an asthma rate more than double that.

Table n° 4: Monte Maiz people with asthma symptoms, n of cases, prevalences and Argentine prevalences

Disease type asthma	n of cases / n surveyed	Monte Maíz prevalence	Argentine prevalence
I all surveyed	803 / 4957	16,2%	
Smoker >16 years old	122 / 531	22%	75% in Argentina
History of prematurity	35 / 803	4,3%	
In 18 - 40 years old	233 / 1853	12,6%	5.9% MsaI **
Children of 13 and 14 years old	57 / 143	39,9%	12.5% (ISAAC)***
Children of 6 and 7 years old	86 / 164	52,4%	16.4% (SAP)****

\* Bibliographic reference 23; \*\* Bibliographic reference 19, \*\*\* Bibliographic reference 21, \*\*\*\* Bibliographic reference 22.

Using a methodology identical to that employed in this study (21), ISAAC reports an asthma prevalence of 13.6% for children aged 13-14 years (20). The most recent publication of the Argentine Society of Pediatrics recognizes a national prevalence of 16.4% in children aged 6-7 years and 10.9% in those aged 13-14 years (9). Among the 307 children surveyed in Monte Maíz the prevalence of asthma is three times higher (52.4% and 39.9% for the 6-7 year-old group and 13-14 year-old group respectively)(see Table 4).

Confounding variables such as smoking and premature birth were not linked to asthma in any of the statistical methods applied. For example, smoking was present in 22% of the residents of Monte Maíz who use bronchodilators, but in up to 75% in studies of asthma and wheezing in the city of Buenos Aires (22). In Monte Maíz, the inhabitants directly linked to agriculture no correlation with asthma arose, and the affected inhabitants were residential reflecting environmental exposure and no occupational exposure.

The high prevalence of asthma in this population with heavy exposure to glyphosate and other pesticides is consistent with the strong link between pesticides and asthma (23,24) including recent studies which specifically link glyphosate with asthma (25,26). The cluster of asthma symptoms in sectors R16 and R17, which both receive wind that sheds glyphosate-laden grain dust from silos, suggests a dose-response relationship. These data are congruent with local studies that found a prevalence of wheezing and rhinitis in 49% of people living near the silos (27).

The cause of asthma appears to be a combination of genetic predisposition with infections and / or environmental exposure to inhaled substances and particles (4,5). A cohort study in children with residential exposure to organophosphate pesticides found that they damage lung function as much or more than cigarette smoke (28). In the Children's Health Study, early exposure to herbicides increased the risk of asthma 4.5 times (29) and a recent ecological study of organic farms vs. conventional farms (those using pesticides) found more wheezing in children living on or near conventional farms (30).

Low molecular weight chemicals, such as herbicides, can induce occupational asthma (31). According to Jarvis' SAR (structure-activity relationship) model, the glyphosate risk index is 0.6257, which supports its potential to induce asthmatic symptoms (32).

Experimental studies on the effects of inhalation of glyphosate in rats indicated that it caused wheezing, reduced ciliary activity, and produced thick nasal secretion even at low levels of exposure, according to studies dating back more than 20 years, before its current levels of heavy use (33,34). More recently Kumar et al. demonstrated that rats exposed to glyphosate-rich

air samples (collected on farms or air with added glyphosate) display increased eosinophil and neutrophil counts, mast cell degranulation, and interleukin production in their airways, confirming the role of glyphosate in the pathogenesis of asthma (35).

In short, previous studies provide plausibility to the findings of this study: a high prevalence of asthma in a population environmentally exposed to glyphosate. The weakness of this study is its observational and ecological design, which is insufficient to make categorical causal statements. Nor can it rule out the ecological fallacy. Finally, data from the control population were taken in 2003 and those of Monte Maíz in 2014, although ISAAC phase III did not find significant differences between phase I and phase III also made 10 years later (36).

ISSAC showed wide variability in global asthma rates and in Latin America the range was between 8.6 and 32.1% in children aged 6-7 years or between 6.6 and 27% in those aged 13-14 years (20), but in Monte Maíz it reached 39.9% and 52.4% respectively. Overall, compared to the Argentine cities studied by ISAAC, the data from Monte Maíz express a risk more than 4 times greater (OR: 4.64 with CI of 3.26 - 6.60), which indicates an ecological factor beyond any natural variability of the population.

## V. CONCLUSION

The findings suggest a link between environmental exposure to glyphosate, and to a lesser extent, other pesticides, with high asthma prevalence. This population-environmental study demonstrates the co-occurrence of asthma and environmental exposure to glyphosate, while experimental studies support the plausibility of this association.

### *Conflict of interest:*

The authors declare they have no actual or potential competing financial interests.

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## Quercetin Administration in Adult Patients as a Biochemical Potential against Coronavirus Disease 2019 (COVID-19)

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**Abstract- Aim:** To establishing the use of Quercetin as a nutraceutical potential against Coronavirus Disease 2019.

**Method:** This study is a descriptive, prospective longitudinal that included 52 patients treated at the ECOMED-LAMB Clinic from the onset of Covid-19 in our country, March 3, 2020, to January 2021.

**Results:** Were studied 52 patients COVID-19 positive, 20 (38.4%) were in preventive treatment, and 32 patients (61.5%) biological therapy were administered once the diagnosis; no difference was found between female or male sex and the predominant age was those over 60 years. Twenty-four patients (70.6%) have presented at least one comorbidity.

The association of hospitalization with preventive treatment was not significant ( $p=0.166$ ); we observed a difference during the hospital stay of the patients ( $p= 0.084$ ).

**Conclusions:** Quercetin could prevent and decrease the duration of SARS-CoV-2 infections, it is plausible to propose the prophylactic use of this flavonoid to achieve clinical benefits.

**Keywords:** clinical benefits, flavonoid, biological therapy.

**GJMR-F Classification:** NLMC Code: QW 160



QUERCETIN ADMINISTRATION IN ADULT PATIENTS AS A BIOCHEMICAL POTENTIAL AGAINST CORONAVIRUS DISEASE 2019 COVID 19

Strictly as per the compliance and regulations of:



RESEARCH | DIVERSITY | ETHICS

# Quercetin Administration in Adult Patients as a Biochemical Potential against Coronavirus Disease 2019 (COVID-19)

Juan Fernando Ibarra Aguilar <sup>α</sup>, Gabriela Ariane Sanabria Báez <sup>σ</sup> & Fernando Galeano <sup>ρ</sup>

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## 1. INTRODUCTION

It is known that the COVID-19 is caused by the novel coronavirus SARS-CoV-2, has challenged the health systems and the economy of all countries affected by the pandemic that worldwide until December 2020 has been diagnosed in 93 million individuals and claimed the lives of 2 million people, the most affected countries had been the United States of America, India and at the regional level Brazil (1) with 45% of all cases.

Mortality estimates vary according to the country, and the data reported ranges from less than 0.1% to more than 25% (2); these data have mobilized many researchers in the identification of drugs against this pathology, either as therapeutic or prophylactic for the treatment, or control of viral infection.

In this race against COVID-19, the reuse of numerous drugs has been implemented, with different mechanisms, as well as the use of medication with applications other than antiviral action (3); in this line, some research groups have reported the promising

therapeutic effects of hydroxychloroquine or chloroquine, remdesivir (novel antiviral nucleotide analog), lopinavir, and ritonavir against severe COVID-19 (4).

In the fight against diseases and more, when we speak of a pandemic, we have the option of starting a preventive or prophylactic treatment to reduce the incidence or severity of the disease and the public expenditure of the disease (5). However, drug prevention and control are still controversial, without considering the possible adverse effects in some cases, such as hydroxychloroquine or chloroquine (6), then. The use of biochemicals is an alternative that may be imposed in these cases as COVID-19 chemoprophylaxis. Quercetin (3,3',4',5,7-pentahydroxy flavone) is a plant flavonoid found in various vegetables, leaves, seeds, and grains, where it conjugates with residual sugars to form quercetin glycosides (7) has action known as an antioxidant with anti-inflammatory and antiviral bioactive that acts by inhibiting the entry of viruses and the fusion of viral cells (8) it is known that reduces the pro-inflammatory expression of cytokines and lung inflammation caused by rhinovirus in mouse (9), studies in which Prediction models were applied, it has been seen that quercetin binds to the S protein of SARS-CoV-2 in the host receptor region or to the interface of the human S-ACE2 protein, which interferes with the entrance into the cells of the virus. Cells, this reveals its therapeutic potential (10) and supports the idea that it inhibits infection by the SARS-CoV virus (11). Other authors also found that quercetin combined with vitamin C induces synergistic antiviral and immunomodulatory effects against COVID-19 (12).

The mode of action of vitamin C as an antiviral is supported by the activity of lymphocytes, increasing the production of interferon- $\alpha$ , modulating cytokines, reducing inflammation, improving endothelial dysfunction, and restoring mitochondrial (13) and viricidal function (13-14).

In this study, we collect scientific evidence of the use of quercetin and vitamin C, vitamin B2B3B5, and ZINC for ATP formation, the use of Copper as an iron stabilizer for the prevention and treatment of the SARS-CoV-2 / COVID-19 Pandemic with the objective of establishing the use of Quercetin as a nutraceutical potential against coronavirus disease 2019 (COVID-19).

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## II. MATERIALS AND METHODS

A descriptive, prospective work was carried out. Of a total of 75 patients followed up by biweekly or monthly consultation until the disappearance of the clinical and radiological findings in the ECOMED-LAMB Clinic, 52 patients were included in the period from the beginning of Covid-19 in our Country, March 3, 2020, to January 2021.

As inclusion criteria, patients of legal age with a diagnosis confirmed by PCR or symptomatic direct contact with COVID-19 in the period studied was considered, and patients with incomplete data were considered exclusion criteria.

Age, sex, underlying disease, and hospitalization requirement was studied.

Also, the start of treatment before, at, or after the diagnosis of COVID-19 and the time of improvement was specified.

Was made a descriptive analysis of variables using frequency distribution and percentages. To

establish possible associations between evolution and biological treatment was used Chi-Square test.

The research ethics committee of the Institute of Tropical Medicine had approved the study, and the information obtained was kept confidential and used only for scientific purposes.

## III. RESULTS

In this study, patients with preventive treatment of quercetin, vitamin C, zinc, and Copper were initially included, in addition to a vitamin revitalizer composed of Vitamin B1, B2, B3, B5, B9 and B12, Mg, Zinc, and Copper. Finally, 52 patients diagnosed with COVID-19 have studied, 20 patients (38.4%) was in preventive treatment and 32 patients (61.5%) was administered biological therapy once the diagnosis obtained, the demographic characteristics are demonstrated in Table 1.

**Table 1:** Demographic characteristics of adult patients with quercetin administration as a biochemical potential against coronavirus disease 2019 (COVID-19). Year 2020

Demographic characteristics	N= 52	%
<b>Gender</b>		
Female	24	46.15
Male	28	53.85
<b>Grouped age</b>		
20 - 29 years	4	7.69
30 - 39 years	9	17.31
40 - 49 years	12	23.08
50 - 59 years	9	17.31
> 60 years	18	34.62

Regarding comorbidity, which includes: cancer, heart disease, diabetes, obesity, respiratory, puerperal, 24 patients (70.6%) have presented at least one comorbidity and ten patients (29.4%) two of those mentioned, with a total of 34 patients (65%) with some risk factor.

About biological treatment, preventive treatment, and the beginning of it, we can see in Table 2 the details of the same, and the observed evolution.

**Table 2:** Administration of quercetin in adult patients as a biochemical potential against coronavirus disease 2019 (COVID-19). Year 2020

Variables	N= 52	%
<b>Biological treatment</b>		
Immunocu	43	84.69
Immunocu + Revitalizer	4	7.69
Immunocu + Revitalizadorcu	3	5.77
Revitalizing	1	1.92
<b>Vitamin C, Zinc and D3</b>		
Start of treatment	20	38,4
Before the diagnosis of COVID-19	32	61,5

After the COVID-19 diagnosis	14	26.92
With other preventive treatment		
Evolution	1	1.92
Asthma	2	3.85
Pneumonia	4	7.69
24-hour oxygen requirement	6	11.54
Asymptomatic	39	75.00
Improved	4	7.69

The association of hospitalization concerning preventive treatment was not significant ( $p = 0.166$ ). We have observed a difference in terms of the evolution of the patients with a  $p = 0.084$  (Table 3).

**Table 3:** Relation of hospitalization and evolution with Quercetin administration in adult patients as a biochemical potential against coronavirus disease 2019 (COVID-19). Year 2020

Variables	Previous biological treatment		p
	No n=32 (61.5%)	Yes n=20 (38.4%)	
<b>Internment</b>			
Yes	4 (12.5)	6 (30)	0.156
No	28 (87.5)	14 (70)	
<b>Evolution</b>			
Improved	24 (75)	15 (75)	0.035
Oxygen requirement	4 (12.5)	0	
Pneumonia	2 (6.25)	0	
Asymptomatic	1 (3.1)	5 (25)	
Asthma	1 (3.1)	0	

Regarding the evolution of the patients, we have observed that preventive treatment before contracting Covid-19 causes patients to present mild symptoms. Those who started treatment between days 1 to 6 of the confirmation of the Covid-19 diagnosis, had symptoms mild to moderate and improved within 48 hours to mild symptoms.

Patients who had Covid-19 and started treatment on day 7 or 8 of the symptoms improved after 4 to 6 days; two of them was hospitalized.

All received outpatient treatment except for two of them who began treatment with moderate to severe symptoms and required hospitalization.

#### IV. DISCUSSION

Nutraceuticals include any food or part of food that provides health benefits, including the prevention or treatment of disease. Quercetin is a nutraceutical compound with a well-known preventive activity against viral respiratory infections. Quercetin, used orally is considered safe because has low toxicity (15). Also in 1998, was evaluated the carcinogenic effect of quercetin by the International Agency for Research on Cancer, and assigned it to Group 3 mutagenicity, suggesting the absence of carcinogenicity in humans at safe doses (500 mg twice daily for 12 weeks) (16).

Studies have shown that quercetin is active against several viruses, including human immunodeficiency virus (HIV) (17), herpes simplex virus (type 1 and 2) (18), poliovirus (type 1) (19), parainfluenza (type 3) (20), hepatitis C virus (21), respiratory syncytial virus Sindbis virus, vaccinia virus and coronavirus (SARS-CoV) (22). Also, oral quercetin has been described in two studies used as a prophylactic against respiratory viruses, such as avian influenza (H5N1), and rhinovirus (17).

COVID-19 occurs with greater severity in patients with advanced chronological age (5). As reflected in our study where the highest proportion of affected is among those over 60 years of age, in terms of sex, we have not found any relevant difference.

Coronary heart disease and diabetes are common comorbidities in patients with COVID-19, just as SARS and MERS. In SARS, the prevalence of Diabetes mellitus and cardiovascular disease was 11% and 8%, respectively, and the presence of either of the two comorbidities increased the risk of death 12 times (23-24). Several studies have shown that diabetes mellitus and hypertension were prevalent in approximately 50% of MERS cases (24); on the other hand, cardiovascular disease was present in around 30% of the patients (24). The presence of cardiovascular comorbidities is also valid for COVID-19, especially

among those with more major disease. In a cohort study of 191 patients from Wuhan, China, there was at least one comorbidity in 48% (67% of non-survivors), hypertension in 30% (48% of non-survivors), DM in 19% (31% of non-survivors), and CVD in 8% (13% of non-survivors) (25), in our study the presence of at least one comorbidity it was found in 70.6%, well above that reported by Other authors.

At the beginning of the infection, quercetin inhibits the entrance of SARS-CoV-2 into the host cell, what makes it a promising drug for COVID-19 chemoprophylaxis (17). In the recent study by Wang D et al. (26), they showed that the concentration required to suppress at least 50% of SARS-CoV-2 is 83.4  $\mu$ M, this concentration is considerably lower than the concentration achieved in human blood. (418  $\mu$ M for a daily dose of 500 mg for 12 weeks) (21), the biological treatment administered to our patients consists of 300 mg of quercetin, 300 mg of vitamin C, 5 mg of zinc and 0.2 mg copper (Immunocu ©), 53.8% of the patients received this biological compound at the time of confirmation of the diagnosis of COVID-19, without preventive treatment. In 75% of the patients has been seen an improvement, only 3 (5.7%) manifested some respiratory symptoms such as asthma (1 patient) and pneumonia, and 4 (7.7%) required oxygen only for 24 hours and therefore hospitalization, the other patients was treated on an outpatient basis.

No deaths have been recorded in our study group, and the time to improve once the treatment has started and the manifestation of symptoms is three days.

These Reverse Transcriptase Enzymes and 3CL are essential for viral replication and have become a molecular target in the development of anti-SARS-CoV-2 drugs (quercetin blocks two enzymes that are involved in viral replication, one of the reverse transcriptase and 3CLpro which is a protease). Also, because glycosylated quercetin is more soluble and highly bioavailable in the lumen of the intestine (23), its use could be more beneficial than using of the aglycone form, the best intestinal absorption of Quercetin was obtained if it was combined with Vitamin C or Bromelain. There is actually a clinical trial in Turkey, named NCT04377789, titled "Quercetin for the prophylaxis and treatment of COVID-19". This study says that quercetin's strong antioxidant and anti-inflammatory activity accompanies an excessive immune reaction in severe cases, making it effective in both to prevent and treat of COVID-19.

## V. CONCLUSIONS

Due to the results obtained, we can say that quercetin could prevent and decrease the duration of SARS-CoV-2 infections, so it is plausible to propose the prophylactic use of this flavonoid to achieve clinical

benefits. Although these tests are preliminary due to the sample's size, it would be interesting to confirm them through in vitro tests and subsequently in a randomized clinical trial.

Despite this, given the clinical evidence of this study and the improvement results of patients with positive Covid-19, treated early or at the time of acquiring the disease, initial positive Covid-19 symptomatic patients without symptoms of severe hypoxia, we see that quercetin therapy and revitalizing vitamin compounds could be used on an outpatient basis.

Severe symptoms shorten the use of oxygen and, in 24 to 72 hours, improve its saturation.

This form of treatment can be of preventive and coadjuvant use in severe cases, reducing hospital stay.

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### Conflict of interests

The authors declare that they have no competing economic interests or personal relationships that could influence the work reported in this article.

### Author contributions

All listed authors have made a substantial, direct, and intellectual contribution to the work and have approved it for publication.

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## The use of 4-Demethyl-4-Cholesteryloxypenclomedine [DM-CHOC-PEN] as Therapy in Adolescent and Young Adult (AYA) Subjects with Advanced Malignancies Involving the Central Nervous System (CNS)

By Morgan, LR, Weiner, RS, Ware, ML, Bhandari, M,  
Mahmood, T & Friedlander, P

**Introduction-** In 2020 about 89,000 adolescents and young adults (AYA) (ages 15 to 39) were estimated to be diagnosed with cancer in the United States, 23,890 had CNS and spinal nervous system (SNS) involvement—accounting for one twentieth or five percent of the number cancer diagnoses in the United States. The estimated deaths for this group was 18,020 deaths in 2020 (1).

This, is about eight times the number of cancers diagnosed in children ages 0 to 14 (2).

The National Cancer Institute (NCI) and the American Cancer Society (ACS), in conjunction with the World Health Organization (WHO), EORTC, ECCO, and UK Cancer Foundation estimate that nearly 15% of CNS and SNS tumors worldwide involve the adolescent/ young adult (AYA) age group (3, 4).

**GJMR-F Classification:** NLMC Code: QZ 20.5



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# The use of 4-Demethyl-4-Cholesterylloxypenclomedine [DM-CHOC-PEN] as Therapy in Adolescent and Young Adult (AYA) Subjects with Advanced Malignancies Involving the Central Nervous System (CNS)

Morgan, LR <sup>α</sup>, Weiner, RS <sup>σ</sup>, Ware, ML <sup>ρ</sup>, Bhandari, M <sup>ω</sup>, Mahmood, T <sup>¥</sup> & Friedlander, P <sup>§</sup>

## INTRODUCTION

In 2020 about 89,000 adolescents and young adults (AYA) (ages 15 to 39) were estimated to be diagnosed with cancer in the United States, 23,890 had CNS and spinal nervous system (SNS) involvement—accounting for one twentieth or five percent of the number cancer diagnoses in the United States. The estimated deaths for this group was 18,020 deaths in 2020 (1).

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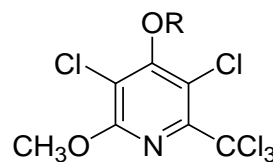
The most common types of cancer involving the CNS and SNS diagnosed in the AYA population are primary brain tumors (glioblastoma (GBM), astrocytoma, etc.) and metastatic cancers – *melanoma, leukemia, and sarcoma* (2, 3, 5).

For both male and female individuals <20 years of age, primary and secondary cancers of the CNS and SNS are the most common causes of death from cancer. In the 20-39 year age group, CNS/SNS cancers are the first cause of cancer-related deaths in males and the fifth cause of cancer-related deaths in females (2). Overall, in the 15 - 39-year old range – 5-year survivals have remained stagnant since 1995. However, for individuals aged 30 to 34, survival rates have decreased (2). The incidence and histology of cancer types do vary according to subject age and gender (2, 3).

Results from surgery and radiation for localized non-invasive cancers are encouraging for all ages, including AYAs. However, for advanced disease, unless a tumor possesses a phenotypic target or a genetic mutation, the long term outlook for survival beyond one year are limited (4). Yes, the standard of care—chemotherapy, and radiation provide responses with improved survival; however, the long-range prognosis is still not 100% (4). Unfortunately, AYA aged individuals with advanced CNS involvement do not have a good prognosis (5).

The AYA aged group of individuals with malignancies deserves special attention since they generally lack histories of comorbidities. This age group are still at risk for toxicity with immune chemotherapy regimens in current use. AYA individuals with cancer also demonstrate different host biology, tumor pathophysiology (2, 4). They metabolize chemotherapy drugs differently than do either younger or older individuals (2, 4). Unfortunately, there are few AYA oncology specialists available (6).

Weiner *et al* presented early Phase I results and experiences with 4-demethyl-4-cholesterylloxypenclomedine (DM-CHOC-PEN) as a treatment for AYA individuals with cancers involving the CNS (6). Encouraging responses are reported for the use of DM-CHOC-PEN in AYA subjects in *Table 1* without Gr-3/4 toxicities. The Phase II clinical trials with DM-CHOC-PEN continue (6, 8).



**Fig. 1:** Penclomedine analogs – PEN (R=CH<sub>3</sub>); DM-PEN (R=H); DM-CHOC-PEN (R= CO<sub>2</sub>-cholesteryl)

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Table 1 reviews the AYA subjects treated to date with intravenous doses (39, 55, or 97.8 mg/m<sup>2</sup> of DM-CHOC-PEN administered once every 21 days), along with their responses and toxicities. To date, nineteen (19) subjects in the AYA age group with advanced, chemo-resistant stage IV cancer- melanoma, NSCLC, breast, acute lymphocytic leukemia, oligodendroglioma, or astrocytoma have been enrolled and treated (7, 8).

Unlike patients treated with other penclomedines (PEN, NSC 338720, Fig.1), DM-CHOC-PEN is non-neurotoxic (7). DM-CHOC-PEN crosses the blood-brain barrier (BBB) with responses observed in AYA subjects with sarcoma, astrocytoma, melanoma, ALL, lung, and breast cancers involving the spinal and central nervous systems- Table 1. The drug has been identified and measured in human sarcoma and lung cancer tissues (in concentrations of 61-120 ng/g of tumor

tissue) involving the CNS and not detected in adjacent normal brain tissue (7, 8).

DM-CHOC-PEN does not require hepatic activation and is active *invitro* in nanogram quantities- melanoma GBM, non-small cell lung cancer (NSCLC), and breast cancer explants (7, 8). The drug does not require hepatic activation, which is in contrast to other penclomedines - DM-PEN (Fig. 1) and other analogs (7). These observations have led to a proposed mechanism whereby DM-CHOC-PEN associates with erythrocyte membrane surfaces, penetrates the BBB and brain parenchyma and transported into intracerebral tumors with L-glutamine, with which it shares common structural moieties (7). Thus, DM-CHOC-PEN may be multifunctional - killing micro-metastases, inhibiting DNA repair and inducing an 'abscopal' immune-type effect (7, 8). The latter mechanism of action continues to be supported (9).

Table 1: AYA Subjects with Advanced Cancers Treated with IV DM-CHOC-PEN<sup>++</sup>

Cancer Type (#)	Age/Sex	Dose (mg/m <sup>2</sup> )	Responders w/ CNS (#)	OS (w/CNS) (mos)	Toxicity
Breast (4)	33/F	50	1	12	None
	32/F	50	0	3	None
	30/F	39	0	4	None
		98	0	3	None
Pontine glioma (1)	22/M	50	NR	4	None
Melanoma (1)	39/F	75***	0	3	None
Gastric (1)	19/F	75***	NR	3	None
GBM (4)	36/M	50	NR	5	None
	34/F	75	NR	4	Nausea (Gr-2)
	34/F	98.7	NR	2	None
	24/F	75	Stable Too soon	3	None
	24/M	75			None
ALL (1) NHL (1)	39/M	98.7	CR	8**	None
	28/F*	98.7	No response	6	None
Oligoastrocytoma (1)	39/M	98.7	NR	3	No
Oligodendroglioma (1)	34/F	85.8	NR	4	None
Astrocytoma (1)	31/M	98.7	1	59	None
Lung cancer (NSCLC) (1)	39/F	98.7	1	69+	Vasogenic edema (Gr-2)
H & N (1)	32 (M)	98.7	NR	6	None
Melanoma (1)	34 (F)	98.7	NR	3	None

\*No CNS disease & no responses; \*\*CNS – CR, w/peripheral progression; \*\*\*Liver disease (malignant or chronic)

\*\*DM-CHOC-PEN was administered IV once every 21-days; \*No CNS disease – no responses; \*\*CNS – CR, w/ peripheral progression

The pharmacokinetic profile for DM-CHOC-PEN in the AYA subjects with a lower T<sub>1/2β</sub> – 28:71 h reflects a 'healthier' metabolic profile for the drug compared with older adults, who may have been receiving medications for associated comorbidities resulting in induced hepatic metabolic activity (9).

Moreover, AYA subjects– 15-39 years old – are of major interest since they are not commonly enrolled in clinical trials and typically managed by pediatric and adult oncologists, rather than AYA oncology specialists who also appreciates the physical, psychosocial, emotional, sexual, spiritual, financial, dietary, etc.



peculiarities of this age group and, therefore apply specialized knowledge to their care (10, 11).

A Phase II clinical trial with DM-CHOC-PEN in AYA subjects (15-39 years old) with malignancies involving the CNS is in progress to validate and expand the observations in *Table 1* [IND 68,876] (12).

A blog is now available to follow the clinical trial's progress and information generated for the AYA population (12).

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## A Study on Obesity and Cardiovascular Risk Assessment among the Bengali Hindu Caste Population and Tribal Population of Birbhum District, West Bengal, India

By Aditi Munmun Sengupta, Diptendu Chatterjee & Rima Ghosh

*University of Calcutta*

**Abstract-** Obesity has been considered a complex and multifactorial disease that has almost affected one-third of the total world's population. The present trend related to obesity has revealed that nearly 38% of the adults of the world's population will suffer from the issues of being overweight by the year 2030. As per the ICMR-India study in the year 2015, the prevalence rate of obesity in India varies between 11.8% to 31.3%. The risk of cardiovascular diseases is prevalent around the world, and estimated CVD cases in the year 2015 were approximately 422.7 million, causing 17.6 million deaths (32% of global deaths) as per WHO statistics in 2016. The Indian health data of 2017 has revealed that 25.27% of the population have suffered mortality rate due to the occurrence of CVD in India. Hence, the implementation of health programs for identifying the community risk factors for preventing these diseases has evolved.

**Keywords:** cardiovascular, prevalence, tribal, west bengal, socio-economic, non-communicable diseases, population.

**GJMR-F Classification:** NLMC Code: WG 120



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# A Study on Obesity and Cardiovascular Risk Assessment among the Bengali Hindu Caste Population and Tribal Population of Birbhum District, West Bengal, India

Aditi Munmun Sengupta <sup>α</sup>, Diptendu Chatterjee <sup>σ</sup> & Rima Ghosh <sup>ρ</sup>

**Abstract-** Obesity has been considered a complex and multifactorial disease that has almost affected one-third of the total world's population. The present trend related to obesity has revealed that nearly 38% of the adults of the world's population will suffer from the issues of being overweight by the year 2030. As per the ICMR-India study in the year 2015, the prevalence rate of obesity in India varies between 11.8% to 31.3%. The risk of cardiovascular diseases is prevalent around the world, and estimated CVD cases in the year 2015 were approximately 422.7 million, causing 17.6 million deaths (32% of global deaths) as per WHO statistics in 2016. The Indian health data of 2017 has revealed that 25.27% of the population have suffered mortality rate due to the occurrence of CVD in India. Hence, the implementation of health programs for identifying the community risk factors for preventing these diseases has evolved. The present study deals with the analysis comparing the prevalence of obesity and CVD risk assessment among the Bengali Hindu caste population and the tribals of Birbhum district of West Bengal. To fulfil this objective, a cross-sectional study has been conducted between November 2018-March 2019, which included 127 Hindu Bengali Caste (94 males and 33 females) and 27 tribal (12 males and 15 females) populations, the selection is done by stratified random sampling from Birbhum district of West Bengal. Discrete anthropometric parameters for assessing overweight-obesity and CVD risks have been involved in this study. Descriptive statistical tools and Chi-squared test, Independent t-test, and Pearson's correlation have been used for examining the collected data. The analysed result revealed that the Bengali Hindu caste population is tending more to obesity, which entails the Caste population to be more under threat for CVD risk than the tribals. The results highlight the need to refrain from adopting a 'one size fits all' policy approach in addressing the overweight-obesity epidemic facing India.

**Keywords:** cardiovascular, prevalence, tribal, west bengal, socio-economic, non-communicable diseases, population.

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## I. INTRODUCTION

In today's era, the majority of the population is suffering from a double health burden of diseases, which mainly occurs due to infection and nutrition along with the occurrence of chronic non-communicable diseases (NCDs). The increasing modernization has evolved changes in the lifestyles of the people along with changing diets, which results in the happening of non-communicable diseases such as diabetes, cardiovascular diseases, etc. The reports have revealed that the substantial proportion of death has been caused due to the impact. It can be said that almost 50% of the end of life and approximately 62% of the total disease burden has been attributed to suffering from NCDs in India (Patel et al., 2011). Hence, the emergence of cardiovascular diseases is the NCDs, which have been considered as an utmost concern towards public health (Bhagyalaxmi et al., 2013).

Obesity has been known as developing excess body fat mass, causing adverse effects on healthy metabolism such as the increased risk of morbidity and reduction in life expectancy (Schwartz et al., 2017; Zhang et al., 2014). The health records concerning obesity reveal that roughly 1.9 million adults suffered from the issues of overweight in the year 2016 and approximately 650 million population have the occurrence of obesity (WHO, 2018). The development of obesity is considered multifactorial, affecting the lifestyle and environment of living, and is associated with comorbidities involving cardiovascular diseases, hypertension, sleep disorders, etc. (Zhang et al., 2014; Leite et al., 2009).

Obesity is known as an independent risk factor for the occurrence of cardiovascular diseases (CVDs). The primary cause of occurrence of this disease involves insulin resistance, hypertension, dyslipidaemia among adults and children (Barroso et al., 2017; Akil & Ahmad, 2011). Several studies have shown a correlation between obesity and cardiovascular diseases that majorly involves coronary disease, cardiac arrhythmias, heart failure, and cardiac arrest. The rapid increase in cardiovascular diseases has been observed due to the



correlation of obesity with other diseases such as sleep syndrome, diabetes, hypertension, etc. (Poirier et al., 2006). Hence, CVD has been estimated to be a vital cause for prevalence of disability and death by the year 2020 (Lavanya et al., 2014). Overweight and obesity are the vital factors correlated with the various cardiovascular risk diseases (Srinivasan et al., 2009). Obesity has also been found to show a correlation with hyperuricemia in the cross-sectional studies which have been conducted recently (Zhang et al., 2017; Duan et al., 2015).

The severity of obesity is assessed by measuring the body mass index (BMI). Still, it does not provide any information concerning the distribution of fat, which is majorly responsible for showing high risk towards cardiovascular risk (Zeller et al., 2008). To fulfil this, clinical measurements such as the calculation of waist/hip ratio, abdominal circumference, etc., are introduced for assessing the obesity in the vital body parts. The studies have revealed that the measurement of the abdominal circumference of above 102 cm among men and above 88cm among women has been considered as central obesity, which leads to the development of increased cardiovascular risks (Yusuf et al., 2004). The measurement concerning the waist/hip ratio above 0.9 among men and above 0.85 among women represents central obesity (Ashwell & Hsieh, 2005).

The modern world has shown progression in developing medication towards curative and preventive health measures. Still, many dwelling in isolation and non-polluted regions are considered to be unaware of modern civilization following their traditional values and beliefs. These are the tribals who are more prevalent towards the non-communicable diseases. The reports have revealed that approximately 4,99,638 cases of non-communicable diseases occurred in 2011 in the regions of West Bengal involving obesity and cardiovascular risks resulting in 11,787 deaths. Hence, various studies have been carried out concerning obesity and cardiovascular risks by analysing the sedentary lifestyle. In consequence, the present study has aims to analyse the inquiry on obesity and cardiovascular risk assessment among the Bengali Hindu Caste Population and Tribal Population of Birbhum, West Bengal.

## II. AIMS AND OBJECTIVES

This section will include the objectives to be studied in the paper which are illustrated as:

- To compare the prevalence of obesity and CVD risk assessment among the Bengali Hindu caste population and tribals of Birbhum district of West Bengal
- To examine various cardiovascular-related risk factors such as hypertension, elevated fasting blood glucose, obesity, and metabolic syndrome among

Bengali Hindu caste population and tribals of Birbhum district of West Bengal

- To assess the socio-economic and behavioral risk factors associated with obesity and cardiovascular diseases among Bengali Hindu caste population and tribals of Birbhum district of West Bengal

## III. LITERATURE REVIEW

### a) *Impact of obesity and cardiovascular disease among the population of rural India*

India is a developing country, that is majorly suffering from the impact of undernutrition due to poverty. The reports have revealed that approximately more than 135 million of the population are suffering from obesity. The risk of cardiovascular diseases is widespread in the lower levels of rural India and more frequent in rural South India (Ramachandran et al., 2004). The most prone areas that are affected by the risk of obesity and CVDs are the rural regions. The modernization and developmental activities at a larger scale have brought changes in the lifestyle, occupational patterns, and dietary habits of the people dwelling in the rural sectors of India, mainly the tribal communities. This has evolved as considerable health issues among the infants and elderly population of tribal communities progressing the issues such as obesity, CVDs, diabetes, etc. Obesity has been known to be a complex disorder with paramount health risks related to the emergence of CVDs, cancer, stroke, and early death (IIPS, 2007). One of the studies has revealed that approximately 2-3% of the population in rural India are suffering from overweight, mainly the tribal communities (NNMB, 2009). Undernutrition has been considered as the vital factor that affects the health of the individuals dwelling in the rural regions. The studies have revealed that the rate of morbidity and mortality are increasing among the rural zones of the Asian population showing, lower body mass index (BMI), and further accumulation of intra-abdominal fat is developed. Hypertension has been the major indicator for the increasing prevalence of obesity (Flegal et al., 2013). Hypertension has been known as the third most significant risk factor in the South Asian region. India has been found to have 29.8% in rural India (Rizwan et al., 2014). The occurrence of cardiovascular disease is prevalent among 4-5% of adults in rural India. The risk factors of CVDs change the lifestyle that is more prevalent in rural India (Chow et al., 2007).

### b) *Health and demographic profile of Bengali Hindu caste population and Birbhum tribal population of West Bengal*

Several research studies have been carried out on the demographic processes concerning the population health of the individuals. The primary issues evolving the public health and human development in India has been analysed, providing analytical and

interventional aspects. The Society for Health and Demographic Surveillance (SHDS) analyses the primary ownership of the Birbhum population. The funds are provided by the Department of Health and Family Welfare (DoH&FW) of the Government of West Bengal (Ghosh et al., 2015). The demographic process evaluation involves the analysis of fertility transition, migration, and its impact on the health of the population. The scrutiny concerning the access, equality, and utilization of healthcare services, health insurance, and health expenditure are involved in the demographic profile by the healthcare system. The district of Birbhum is situated in the western region of West Bengal and the eastern part of India. This district is often characterized by undulating geographical topography. This district has been reported with a population of 3 502 387, involving 771 inhabitants per square kilometer (RGI, 2013). The population growth rate has been estimated as 16.15% during the year 2001-2011. The females comprise 956 for every 1000 males in this district. The census of 2011 has revealed that almost 29.5% of the population belongs to scheduled castes and 6.9% of them belong to the scheduled tribes. The tribal health in this district was found to be improved by the National Rural Health Mission (Sharma, 2014). The traditional system of medicines and medical pluralism has been implemented for tribal healthcare (Babu & Mishra, 2014).

The Census of 2011 has revealed that the growth rate of population in West Bengal has decreased for the whole population along with the Hindu Muslim community. The decadal growth rate of the Hindu population in West Bengal was found to be 1.1% in (1981-91); 14.2% in (1991-2001); and 10.8 % in (2001-2011). The increased literacy rate among the females and women empowerment are the factors responsible for the steady decrease in population growth rate in West Bengal. Also, the total fertility rate has been found to decline (Ghosh, 2018; Haq & Patil, 2016).

#### c) *Risk factors involved for obesity and cardiovascular disease*

The increasing body weight has been considered as a principal risk factor causing mortality and morbidity from the impact of cardiovascular diseases. Several studies have revealed the fact that the increase in adiposity has affected a large number of populations, which has been measured by evaluating the body mass index (BMI). Hence, being overweight has been considered as one of the vital risk factors for the occurrence of obesity and cardiovascular diseases. The impact of coronary heart disease has been caused due to the primary risk factors involving total cholesterol, blood pressure, prevalence of smoking, and physical activities (Capewell et al., 2010). Other major risk factors for CVDs include the prevalence and intensity of smoking habits among individuals. Obesity among

individuals is mainly caused by the major risk factor of smoking prevalence (Stewart et al., 2009). Hypertension and dyslipidaemia are other significant risk factors that have adverse health impact (Chobanian, 2010). The metabolic syndrome has also been determined among the individuals who are affected by obesity and cardiovascular risks. The risk factors majorly involved in the clustering of CVD involves insulin resistance, central adiposity, pro-inflammatory, and prothrombotic state, along hypertension and dyslipidaemia (Alberti et al., 2009). Obesity has been known as the independent predictor of CVD and majorly involves the risk factors such as a trial fibrillation, congenital heart disease, and pulmonary arterial hypertension (Badheka et al., 2010; Sandhu et al., 2016; Agarwal et al., 2018).

#### d) *Physiological and behavioral risk factors of obesity and cardiovascular disease in rural India*

The impact of obesity and cardiovascular diseases has been considered as the major cause of mortality in India (Prabhakaran et al., 2016). Most of the Indian population of age above 18 years and also some of the children are suffering from high blood pressure and high blood glucose level, which have been considered as the vital risk factors for obesity and CVD (WHO, 2014). The most prevalent behavioural risk factors for obesity and CVDs in rural India involve the lack of physical activities, use of tobacco, and more access to alcohol (Patel et al., 2011). These behavioral risk factors are most commonly found among individuals suffering from hypertension, glucose intolerance, and obesity. The physiological risk factors of obesity and CVDs involve the overweight, disposition of high levels of fats in the body, unhealthy diet, lack of physical activities, etc. (WHO, 2016; Siegel et al., 2008; Fb, 2011). A lower body mass index has been estimated in the population suffering from obesity and CVDs, which has been considered as physiological risk factors. The traditional dietary patterns are changing, which leads to the adaptation of the industrialized and urban food environment (Siegel et al., 2008). These dietary regimens result in increasing the risk by increasing the body weight and central adiposity. The accumulation of visceral adipose tissues has been observed among smokers induced by the sympathetic nervous system activity. Also, the high consumption of alcohol results in excessive calorie intake and obesity.

#### e) *Risk assessment evidences for obesity and cardiovascular diseases*

The identification, prevention, and reduction for the onset of risk factors need to be determined for the risk assessment of obesity and CVDs that leads to morbidity and mortality (Barroso et al., 2017). The risk factors of CVD involve metabolic syndrome (MetS) among obese individuals (Alberti et al., 2009). The early diagnosis of MetS has evolved early detection and increased the risk of CVD. The fall in blood pressure has

yielded the chances of organ damage and increased cardiovascular complications (Agarwal et al., 2018). The mechanism of utmost importance lying under this complication includes the process of dipping that has been determined by the changes taking place in the sympathetic nervous system activity. It has been observed that the increase in the non-dipping among obese individuals implicates the requirement of reducing the BMI and improving the hemodynamic and lipid profiles, which further results in lowering the risk towards chances of organ damage (Badheka et al., 2010; Sandhu et al., 2016). Several pieces of evidence have revealed that the pulse pressure shows a correlation for the morbidity and mortality due to cardiovascular diseases. One of the studies has revealed that an increase in the BMI results in decreasing the large arterial distensibility among obese men (Flegal et al., 2013). The evolving rise in the cases of obesity and CVDs has evolved the requirement of reducing obesity. It can be achieved by suggesting the pathways influencing obesity during the development of cardiovascular outcomes. The reduction of weight and progressing to more physical activities further helps in improving the components of the coronary heart disease risk profile. Appropriate diet and exercise programs help in the prevention of CVD and obesity.

#### IV. METHODOLOGY

The research work followed for this study was quantitative and descriptive.

- Research approach: The data collection approach was quantitative as the researcher had explained the numerical and statistical research approach along with the implementation of the data collection that required conduction of the survey process for analysing the results. This type of research approach was usually implemented for establishing a correlation among the different variables used in the research study, mainly involving the elements grouping, numbering, and their conversion into the measurable models. The research work had also followed a deductive research approach.
- Research design: The research work had followed a descriptive research design. This type of research design was framed for developing new theories and justifying the practices in the same manner. The descriptive research design aimed to describe the outcomes or observations that had evolved from the social point of view. The theories evolved from this research design correlate the existing variables in the research and required a descriptive method.
- Data Collection: This cross-sectional study included 127 Hindu Bengali Caste (94 males and 33 females) and 27 Tribal (15 males and 12 females) populations in the age group between 20-60 years

from the Birbhum district of West Bengal. Anthropometer (Martin's) was used to measure height; Rod compass was used to measure WC and HC, Weighing machine was used to measure weight, OMRON body scanner was used to measure FM and PBF, Sphygmomanometer was used to measure BP, Skinfold calliper was used to measure BSF, TSF, SSSF, SISF. CVD risk score was estimated as a routine risk assessment. A pretested questionnaire was used to record the unalterable risk factors like age, sex, family history of CVD and alterable risk factors like BMI, blood pressure and obesity indices. Data were initially analysed using Microsoft Excel 2007. Men and women of having  $\geq 23$  BMI were considered over-weight obese (Aziz et al., 2014). Men and women with  $>90$  and  $>80$  WC were considered obese (WHO, 2018). Men and women of having  $>0.90$  and  $>0.85$  WHR were regarded obese (WHO, 2018). Men and women with  $>0.53$  and  $>0.49$  WSR were viewed Overweight obese (Ashwell et al., 2005). Men and women having  $>1.25$  and  $>1.18$  CI were observed as obese (Shenoy et al., 2017). The CVD risk score was assessed by a pretested questionnaire and calculated by QRISK 3 – 2018 risk calculator (<https://qrisk.org/three>).

- Data Analysis: Data was analysed using a descriptive statistical tool, the SPSS software, 2018 version. Chi-squared test, Independent t-test, and Pearson's correlation was used to find the associations. The Chi-squared test was used to study the relationship between discrete variables, the independent t-test was used to compare between means and Pearson's correlation was used to find an association between continuous variables. A P-value of  $\leq 0.05$  was considered to be statistically significant.

#### V. RESULTS AND DISCUSSION

The results of the present study is determined by analysing the collected data, which has been represented in table 1 to 10 in appendices. Table 1 shows that the Weight of the Caste population is significantly higher ( $60.77 \pm 13.24$ ) than the Tribal population ( $54.75 \pm 12.19$ ). BMI of the Caste population ( $24 \pm 4.5$ ) is relatively higher than the Tribal population ( $22.59 \pm 3.67$ ), but the difference is not significant ( $p > 0.05$ ). On the other hand, the SBP of the Caste population is  $148.87 \pm 26.63$  & Tribal population is  $130.37 \pm 25.46$ , and the DBP of the Caste population is  $96.03 \pm 17.02$  & the Tribal population is  $84.92$ , both are significantly higher in case of Caste population than Tribal population. Eventually, the MAP of the Caste population ( $113 \pm 19.24$ ) is slightly higher than the Tribal population ( $100.04 \pm 17.12$ ) and the difference is considered to be significant ( $p < 0.05$ ). Whereas WC and

WHR are also higher in the Caste population than the Tribal population but the difference is considered to be not significant ( $p>0.05$ ). WSR is slightly higher in tribal population than caste population but considered to be not significant. Conicity Index is relatively higher in the Caste population ( $1.25\pm0.19$ ) than the Tribal population ( $1.13\pm0.22$ ), and also the difference is considered to be significant ( $p<0.05$ ). Table 2 revealed that the BMI between Hindu caste and tribal population has no significant difference. Table 3 revealed that the WC between Hindu caste and tribal population has no significant difference. Table 4 revealed that the WHR between Hindu caste and tribal population has no significant difference. Table 5 revealed that the WSR between Hindu caste and tribal population has not much significant difference. Table 6 revealed that the Conicity Index between Hindu caste and tribal population has significant differences. Table 7 shows that SBP and BMI are positively correlated for both caste( $r = 0.252$ ) and tribal( $r = 0.303$ ) populations. Still it is significant only for the caste population ( $p<0.05$ ) and 6.03 % SBP can be predicted by BMI of the Caste population. But WHR and WSR, both are positively correlated for caste and tribal populations, but not significant ( $p>0.05$ ). Whereas SBP and WC are positively correlated for both caste( $r = 0.209$ ) and tribal( $r = 0.29$ ) populations, but it is significant only for the caste population ( $p<0.05$ ), and 4.36 % SBP can be predicted by WC of the Caste population. On the other hand, CI shows positive correlation for both caste( $r = -0.078$ ) and tribal( $r = -0.14$ ) populations and not significant ( $p>0.05$ ). Table 8 shows that DBP and BMI were positively correlated for both caste( $r = 0.22$ ) and tribal( $r = 0.33$ ) populations, but it is significant only for the caste population ( $p<0.05$ ) and 4.84 % DBP can be predicted by BMI of the Caste population. But WHR and WSR, both are positively correlated for caste and tribal populations, but not significant ( $p>0.05$ ). Whereas DBP and WC are positively correlated for both caste( $r = 0.26$ ) and tribal( $r = 0.32$ ) populations, but it is significant only for the caste population ( $p<0.05$ ), and 6.76 % DBP can be predicted by WC of the Caste population. On the other hand, CI shows positive correlation for both caste( $r = -0.023$ ) and tribal( $r = -0.16$ ) populations and not significant ( $p>0.05$ ). Table 9 shows that MAP and BMI are positively correlated for both caste( $r = 0.24$ ) and tribal( $r = 0.32$ ) populations. Still it is significant only for the caste population ( $p<0.05$ ) and 5.76 % MAP can be predicted by BMI of the Caste population. But WHR and WSR, both are positively correlated for caste and tribal populations, but not significant ( $p>0.05$ ). Whereas MAP and WC are positively correlated for both caste ( $r = 0.25$ ) and tribal( $r = 0.31$ ) populations, but it is significant only for the caste population ( $p<0.05$ ), and 6.25 % MAP can be predicted by WC of the Caste population. On the other hand, CI shows positive correlation for both caste( $r = -0.14$ ) and tribal( $r = -0.16$ )

populations and not significant ( $p>0.05$ ). Table 10 shows that the unalterable risk score is significantly higher in the Caste population ( $6.16\pm1.28$ ) than in the Tribal population ( $5.37\pm1.44$ ). The alterable risk score is also higher in the Caste population ( $14.74\pm1.96$ ) than the Tribal population ( $13.96\pm1.82$ ), but the difference is considered to be not significant ( $p>0.05$ ). Whereas the total risk score of the Caste population ( $20.9\pm2.51$ ) is significantly higher than the Tribal population ( $19.33\pm2.86$ ).

Rising obesity prevalence in India needs appropriate measures for prevention and management. Obesity characteristics (including ectopic fat) are more adverse in Asian Indians and lead to morbidities at lower BMI levels than white Caucasians. Lifestyle management should be advised at lower limits of BMI and waist circumference according to Indian guidelines (Behl *et al.*, 2017). Pasco *et al.*, 2014, reported that the prevalence of obesity using a BMI threshold might underestimate the true extent of obesity in the white population, particularly among young and older men. They also suggested that optimal sex-and age-specific origins be implemented for defining underweight and obesity in terms of body fat and recognize that such definitions will depend on risk assessment for disease, morbidity, and mortality. Dalvand *et al.*, showed the differences between obesity and WC in urban and rural people of Iran. They reported that Waist circumference (WC) is an indicator of the visceral adipose tissue (VAT). A substantial amount of VAT is related to metabolic syndrome, diabetes, and cardiovascular diseases. According to Czernichow *et al.*, 2011, positive, linear and continuous associations were observed in WC and WHR and cardiovascular outcomes. Tran *et al.*, 2018, found that WC or an index based on WC was more strongly associated with BP, glucose, and TC for Vietnamese men and with glucose for Vietnamese women and provided better discrimination of hypertension. WC is an indicator of central fat accumulation and the amount of intra-abdominal adipose tissue (IAAT), high levels of which confer an increased risk of cardio-metabolic disease. The study of Janssen *et al.*, 2019, provided compelling evidence that BMI coupled with WC did not predict obesity-related health risk better than did WC alone when these two anthropometric measures were examined on a continuous scale, indicating that WC, and not BMI, explains obesity-related health risk.

About the earlier works, the present study reveals that 55.55% of the Caste population ( $n=127$ ) is obese, whereas 25.19% Tribal population ( $n=27$ ) is obese based on Conicity Index, and the difference is significant( $p<0.05$ ). Based on BMI, 58.26% of the Caste population is obese, and 62.96% Tribal population is obese, but the difference is not significant ( $p>0.05$ ).

On the other hand, the Caste population is more obese (38.58%) than the Tribal population



(33.33%) based on WC. More obesity is found among the Caste population (62.20%) than the Tribal population (59.25%) based on WHR. In the case of WSR, obesity is slightly higher in the Tribal population (55.55%) than the Caste population (55.11%). The differences are not significant for BMI, WC, WHR, and WSR between Caste and Tribal populations. Physiological variables like SBP, DBP, and MAP are significantly higher in case of the Caste population than the Tribal population. Whereas, Conicity Index is notably higher in Caste population ( $1.25 \pm 0.19$ ) than Tribal population ( $1.13 \pm 0.22$ ). Weight is significantly higher in the Caste population ( $60.77 \pm 13.24$ ) than the Tribal population ( $54.75 \pm 12.19$ ). SBP, DBP, and MAP are positively correlated with BMI and WC for both the Caste and the Tribal populations, but these are only significant for the Caste population. Cardio-vascular disease risk is significantly higher in the Caste population ( $20.9 \pm 2.51$ ) than the Tribal population ( $19.33 \pm 2.86$ ).

## VI. CONCLUSION AND RECOMMENDATION

According to the present study, it can be concluded that the Caste population tends more to obesity than the Tribal population for WC and WHR as waist circumference is a more accurate measure of the distribution of body fat, and WHR is strongly associated with obesity. The present study also suggests that the overall weight is significantly higher in the Caste population than the Tribal population, which entails that

the Caste population is prone to be overweight hence obesity. Though WC and WHR have continuous associations with Cardio-Vascular disease and WC is strongly associated with BP, the present study also reveals that SBP, DBP, and MAP are significantly higher in the Caste population than the Tribal population. Consequently, Caste population is more under threat in CVD than Tribal population.

Although this study is limited in identifying the contextual factors to obesity and CVD at the macrolevel, the results highlight the need for a targeted approach like community-based lifestyle programs to incorporate the socio-cultural related factors on overweight-obesity control policy implementation. In the present circumstances when India is undergoing a reasonable economic growth and urbanization, there is a massive transition in nutrition patterns and the growing sedentary lifestyle. Both obesity and CVD pose as vital public health challenges for the Indian Government (Siddiqui et al., 2016). There is a need to translate evidence into policy, integrate various policymakers, develop effective policies and modify healthcare systems for effective delivery of preventive care for overweight-obesity and CVD preventive care. Understanding the causal factors that are driving the overweight/obesity pattern and the inter-relationship with CVD risk factors at the individual and large scale, it is critical to implement the appropriate policy strategies.

## APPENDICES

Variables	Caste (n=127) Mean $\pm$ SD	Tribe (n=27) Mean $\pm$ SD
Height (cm)	158.81 $\pm$ 8.97	154.98 $\pm$ 8.01
Weight (kg)	60.77 $\pm$ 13.24*	54.75 $\pm$ 12.19*
BMI	24 $\pm$ 4.5	22.59 $\pm$ 3.67
WC (cm)	83.78 $\pm$ 13.4	79.21 $\pm$ 11.22
HC (cm)	90.69 $\pm$ 12.06	89.08 $\pm$ 8.43
WHR	0.92 $\pm$ 0.13	0.88 $\pm$ 0.06
WSR	0.5 $\pm$ 0.05	0.52 $\pm$ 0.08
PBF	26.42 $\pm$ 9.18	26.41 $\pm$ 6.4
FM	14.63 $\pm$ 5.77	13.52 $\pm$ 5.63
FFM	46.94 $\pm$ 12.88	42.74 $\pm$ 10.55
SBP (mmHg)	148.87 $\pm$ 26.63*	130.37 $\pm$ 25.46*
DBP (mmHg)	96.03 $\pm$ 17.02*	84.92 $\pm$ 13.81*
MAP	113.63 $\pm$ 19.24*	100.04 $\pm$ 17.12*
BSF (mm)	8.26 $\pm$ 2.49	7.72 $\pm$ 3.58
TSF (mm)	10.7 $\pm$ 3.55	10.77 $\pm$ 3.69
SSSF (mm)	18.94 $\pm$ 7.26	17.3 $\pm$ 5.52
SISF (mm)	14.7 $\pm$ 5.1	12.59 $\pm$ 5.55
Sum of 4 SF (mm)	51.97 $\pm$ 18.54	48.4 $\pm$ 15.13
Conicity Index	1.25 $\pm$ 0.19*	1.13 $\pm$ 0.22*
(*p<0.05)		
Degree of freedom – 152		

**Table 1:** Distribution of Anthropometric variables among Caste and Tribal populations

	Caste (n=127) [%]	Tribal (n=27) [%]
Obese	74 [58.26]	17 [62.96]
Non-obese	53 [41.73]	10 [37.03]

**Table 2:** Distribution of obesity on the basis of BMI among the Caste and Tribal populations

	Caste (n=127) [%]	Tribal (n=27) [%]
Obese	49 [38.58]	9 [33.33]
Non-obese	78 [61.41]	18 [66.66]

**Table 3:** Distribution of obesity on the basis of waist circumference among Caste and Tribal population

	Caste (n=127) [%]	Tribal (n=27) [%]
Obese	79 [62.20]	16 [59.25]
Non-obese	48 [37.79]	11 [40.74]

**Table 4:** Distribution of obesity on the basis of WHR among Caste and Tribal populations

	Caste (n=127) [%]	Tribal (n=27) [%]
Obese	70 [55.11]	15 [55.55]
Non-obese	57 [44.88]	12 [44.44]

**Table 5:** Distribution of obesity on the basis of WSR among Caste and Tribal populations

	Caste (n=127) [%]	Tribal (n=27) [%]
Obese	70 [55.55]	7 [25.19]
Non-obese	56 [44.44]	20 [74.80]

**Table 6:** Distribution of obesity on the basis of Conicity Index among Caste and Tribal populations

Correlation of SBP with	Caste population (n=127) <i>r</i>	Tribal population (n=27) <i>r</i>
BMI	0.252*	0.303
WC	0.209*	0.29
WHR	0.11	0.15
WSR	0.159	0.27
CI	-0.078	-0.14

**Table 7:** Correlation of SBP with Anthropometric indices between Caste and Tribal populations

Correlation of DBP with	Caste population (n=127) <i>r</i>	Tribal population (n=27) <i>r</i>
BMI	0.22*	0.33
WC	0.26*	0.32
WHR	0.16	0.21
WSR	0.17	0.24
CI	-0.203	-0.16

**Table 8:** Correlation of DBP with Anthropometric indices between Caste and Tribal populations

Correlation of MAP with	Caste population (n=127) <i>r</i>	Tribal population (n=27) <i>r</i>
BMI	0.24*	0.32
WC	0.25*	0.31
WHR	0.15	0.19
WSR	0.17	0.26
CI	-0.14	-0.16

**Table 9:** Correlation of MAP with Anthropometric indices between Caste and Tribal populations

CVD risk score	Caste population (n=127) Mean $\pm$ SD	Tribal population (n=27) Mean $\pm$ SD
Unalterable risk score	6.16 $\pm$ 1.28*	5.37 $\pm$ 1.44*
Alterable risk score	14.74 $\pm$ 1.96	13.96 $\pm$ 1.82
Total risk score	20.9 $\pm$ 2.51*	19.33 $\pm$ 2.86*

**Table 10:** Distribution of CVD risk score estimation among Caste and Tribal populations

# Unalterable risk factors-age, gender and race, family history of CVD to determine the genetic predisposition.  
## Alterable risk factors- Body mass index(BMI), blood pressure, obesity indices.

#### Pretested Questionnaire

**NAME:** **AGE:** **SEX:**  
**EDUCATION:** **OCCUPATION:** **NO. OF FAMILY MEMBERS: ADULT:** M- F-  
**CHILDREN:** M- F-  
**NO. OF ROOMS IN HOUSE:**  
**SMOKING HABIT:** BIDI - CIGERETTE - LOCAL ANY OTHER - **STARTING AGE -**  
**ALCOHOL INTAKE:** (DAILY / MONTHLY / WEEKLY / OS) **STARTING AGE-** GUTKHA- PAN- OTHERS-  
**PHYSICAL WORK FOR HOUR -** **TYPE OF WORK -**  
**ANY INFECTIOUS DISEASE -** **ANY DEATH CASE IN LAST 5 YRS -**  
**DIABETIC DURATION / FAMILY HISTORY- (M / F)**  
**HAVE ANY DISAEASE -** **HOW MANY YEARS -** **CVD DURATION / FAMILY HISTORY- (M / F)**  
**ANY MEDICATION, MEDICINE INTAKE -** **REASON: HYPERTENSION / DIABETES / CVD / OTHERS**

#### ANTHROPOMETRY:

**HEIGHT:** **WEIGHT:** **WC:** **HC:** **WHR:**  
**FM:** **FFM:** **NC:** **SITTING HEIGHT:**  
**BI-ACROMIAN:** **BI-ILLIAC:**  
**PULSE:** **BLOOD SUGAR:**  
**OXYGEN SATURATION:** **SBP:** **DBP:** **MAP:**

#### SEGMENTAL FAT DISTRIBUTION:

**BMI:** **PBF:** **BODY AGE:** **RM:** **VF:**  
**SUBCUTANEOUS:** **WHOLE BODY-** **TRUNK-** **ARM-** **LEG-**  
**SKELETAL:** **WHOLE BODY-** **TRUNK-** **ARM-** **LEG-**

#### SKINFOLD MEASUREMENTS:

**BICEPS:** **TRICEPS:** **SUB-SCAPULAR:** **SUPRA -ILLIAC:**

## Abbreviations

BMI- Body mass index  
BP- Blood pressure  
BSF- Biceps skin fold  
CI- Conicity index  
CVD- Cardiovascular disease  
DBP- Diastolic blood pressure  
FM- Fat mass  
FFM- Fat-free mass  
HC- Hip circumference  
IAAT- Intra-abdominal adipose tissue  
MAP- Mean arterial pressure  
NC – Neck circumference  
NCD – Noncommunicable diseases  
PBF-Percent body fat  
RF – Repetition maximum  
SBP-Systolic blood pressure  
SF- Skinfold  
SISF- Supra-iliac skin fold  
SSSF- Subscapular skin fold  
TC- Thigh circumference  
TSF- Triceps skin fold  
VAT- Visceral adipose tissue  
VF- Visceral fat  
WC- Waist circumference  
WHR- Waist hip ratio  
WSR- Waist stature ratio

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### Conflict of interest

The authors state that the study was conducted for educational purpose only, in absence of any commercial or financial relationships that may give rise to a potential conflict of interest.

### Contribution of authors

AMS- Conceptualized and designed the study, literature search, interpreted the study, prepared first draft of the manuscript, critical revision of the manuscript; DC- Conceptualized the study, Interpretation, critical revision of the manuscript; RG- Literature search, preparation of the manuscript.

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## Tattoo as a Possible Trigger for Autoimmune Syndrome Induced by Adjuvants

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**Abstract-** Autoimmune/Inflammatory Syndromes Induced by Adjuvants (ASIA) syndrome is a group of immune-mediated disorders and symptoms that may appear in genetically predisposed individuals after environmental exposure to external factors, the adjuvants, such as silicone, aluminium and other metals. Sarcoidosis, one of its classic examples, have been previously described following tattoo. However, tattoo ink is still not recognized as one of the adjuvants capable of triggering the ASIA syndrome. To reinforce our theory, we also described a 32-year-old patient that developed arthralgia, sicca syndrome, small fiber neuropathy, and post orthostatic tachycardia syndrome (POTS) after being exposed to extensive areas of tattoos and propose the tattoo ink as a possible trigger for the ASIA syndrome, questioning its safety in individuals genetically prone for autoimmunity.

**Keywords:** tattoo, autoimmune/autoinflammatory syndrome induced by adjuvants, autoimmunity, autoantibodies, ink.

**GJMR-F Classification:** NLMC Code: WD 305



*Strictly as per the compliance and regulations of:*





# Tattoo as a Possible Trigger for Autoimmune Syndrome Induced by Adjuvants

Paula David <sup>α</sup>, Abdulla Watad <sup>σ</sup>, Gilad Halpert <sup>ρ</sup> & Yehuda Shoenfeld <sup>ω</sup>

**Abstract-** Autoimmune/Inflammatory Syndromes Induced by Adjuvants (ASIA) syndrome is a group of immune-mediated disorders and symptoms that may appear in genetically predisposed individuals after environmental exposure to external factors, the adjuvants, such as silicone, aluminium and other metals. Sarcoidosis, one of its classic examples, have been previously described following tattoo. However, tattoo ink is still not recognized as one of the adjuvants capable of triggering the ASIA syndrome. To reinforce our theory, we also described a 32-year-old patient that developed arthralgia, sicca syndrome, small fiber neuropathy, and post orthostatic tachycardia syndrome (POTS) after being exposed to extensive areas of tattoos and propose the tattoo ink as a possible trigger for the ASIA syndrome, questioning its safety in individuals genetically prone for autoimmunity.

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## I. INTRODUCTION

Autoimmune/Inflammatory Syndromes Induced by Adjuvants (ASIA) comprise a group of immune-mediated disorders that flourish in genetically predisposed individuals after environmental exposure to so-called adjuvants [1]. The most described adjuvants related to this syndrome include silicone (i.e. Breast silicone implants), aluminium salts, and other metals and vaccines [2–6]. The removal of these agents tend to lead to an improvement of the symptoms and reduction of the related autoantibodies levels when present [5–7]. The adjuvants are responsible for stimulating both the innate and the adaptive immune system and for activating pattern recognition receptors, increasing the immune response to non-pathological stimuli in a genetically prone subject[8].

Sarcoidosis, Sjogren's syndrome, silicone implant incompatibility, and undifferentiated connective tissue disease (UCTD) are examples of conditions that could be considered to have a common pathogenic mechanism for ASIA syndrome, in which individuals

genetically prone to autoimmunity, such as those with HLADRB1 or having the PTPN22 genes, develop the disorder after being exposed to the external triggers[9–11].

## II. CASE IN POINT

A 32-year-old woman presented with arthralgia in her both wrists, knees and ankles, pain in the Achilles tendon area and morning stiffness of one to two hours everyday, dry mouth and eyes, generalized fatigue, right hand and right hemifacial weakness and hyperesthesia of the right leg that appeared two months ago. She had no fever or skin rashes. Additionally, she complains of headache and blurred vision that started around four months ago, with no photophobia or nausea and vomiting, as well as tachycardia and dizziness when standing up. Her physical examination had no remarkable findings, orthostatic hypotension test was negative, but tachycardia of 125 bpm was detected during the maneuver. On her laboratory examination, she had no outstanding results, including low inflammatory phase markers on her blood and negative ANA, anti-Ro, anti-La and ANCA. Her sacral MRI shows no signs of acute or chronic sacroiliitis or findings compatible with spondyloarthritis, her regular and angio-CT of the head were normal, as well as lumbar puncture (LP). On her brain MRI there was no acute findings, and she was treated with IV hydration and caffeine with partial response. To evaluate her peripheral neurological complaints, a Nerve Conduction Study Electromyogram (NCS-EMG) was performed showing a decreased sympathetic response on her right foot and normal on her right hand, with no signs of large fiber polyneuropathy or radiculopathy, that may be compatible with small fiber neuropathy, requiring a skin biopsy for confirmation. When looking for circulating autoantibodies against G protein-coupled receptors of the autonomic nervous system, she had high levels of antibodies against beta1adrenergic receptor, Beta 2 adrenergic receptor and M3 acetylcholine receptor.

On her medical background, she had a previous diagnosis of Crohn's disease (CD), made two years ago, when she had fatigue, generalized arthralgia and diarrhea, positive Anti-saccharomyces cerevisiae antibodies, colonoscopy and capsule endoscopy with signs of inflammation in the terminal ileum and confirming biopsy for CD. At the time, it was started treatment with Prednisone 40 mg, with partial

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improvement. Biological therapy with Vedolizumab was recommended, but the patient refused the treatment. She had no CD symptoms until four months ago when she had disease flare with diarrhea and abdominal pain, treated with steroids. In addition to CD, her past medical history is positive for depression and anxiety, treated with selective serotonin receptor inhibitor, endometriosis and deep venous thrombosis in her right arm in 2017, treated with clexane for three months.

The patient works as a tattoo artist and has personally done extensive tattoos on her own (Fig. 1-4). Before her tattoos, she had no symptoms.

#### a) Aluminium and other metals and tattoo

Interestingly, aluminium salts and other metals were described as components of different colors of tattoo ink [30]. Specifically, the aluminium salts were described as ingredients of the violet ink. Our patient, that had no symptoms previous to her first tattoo, has various and extensive tattoos, including some with violet ink (Fig. 1-4). The presence of aluminium in ink could explain the mechanism through which tattoo may lead to ASIA syndrome, as observed in the described patient.

#### b) Sjogren's syndrome and Tattoo

Sjogren's syndrome (SS) is an autoimmune condition in which salivary and lacrimal glands inflammation lead to a glandular dysfunction, resulting clinically in dry eyes and mouth and commonly other extra-glandular manifestations, including arthralgia [12]. It can be primary or secondary to other autoimmune conditions, such as rheumatoid arthritis [12]. Our patient presented to us with generalized arthralgia, as well as dry mouth and eyes with a positive Schirmer test. Even though SS is considered one of the classic examples of ASIA syndrome[9], there are no reports in the literature that associate those symptoms with the presence of tattoo pigments. Sarcoidosis, on the other hand, another classic manifestation of ASIA syndrome, had been previously associated with the presence of tattoos[13–15].

#### c) Sarcoidosis and Tattoo

Sarcoidosis is a systemic granulomatous pathology of still unclear etiology that develops when a prone individual is exposed to an antigen capable of inducing Th1 immune response and consequent granuloma formation in different organs, including mainly the lungs and lymph-nodes [16]. Infections, autoantigens and inorganic compounds were already described as common triggers[17]. A 29-year-old man had been reported to develop systemic sarcoidosis after tattoo. He had pleuritic chest pain, dyspnoea and cough. On physical examination, there were papules over his tattoo areas and bilateral basal crackles on lung auscultation. Chest X-ray showed bilateral lymphadenopathy and reticulonodular opacities. In the

skin biopsy, noncaseating granulomas with black tattoo pigments were observed[15].

Systemic sarcoidosis and granulomatous reaction without sarcoidosis were previously described in more than 30 patients following permanent tattoo, in the presence or absence of uveitis [13]. It is well known that sarcoidosis granulomas tend to develop in previous scars sites, explaining the finding of granulomas in the tattoo areas in those patients [15]. Interestingly, three tattooed patients were described with isolated eye inflammation, which included posterior uveitis, panuveitis and retinal vasculitis, without other manifestations or granuloma formation elsewhere [18–20]. This may suggest that tattoo ink contains a specific antigen that could stimulate the immune response, locally seen by granuloma formation in the tattoo area or other systemic inflammatory manifestations such as uveitis. A vitreous biopsy performed in a patient with tattoo-associated uveitis showed no tattoo pigment or granulomas, but infiltration of T-lymphocytes with atypia, supporting the explanation of this symptom occurring due to an autoinflammatory/immune reaction [21].

#### d) Post Orthostatic Tachycardia syndrome, ASIA syndrome and tattoo

Our patient also presented with tachycardia and dizziness when standing up. Post-orthostatic Tachycardia syndrome (POTS) is a clinical condition in which patients present with tachycardia and discomfort symptoms when assuming the orthostatic position, without hypotension. The orthostatic tachycardia is described as an elevation of 30 bpm from the heart rate measured before standing or maintaining the heart rate, within 10 minutes of standing, superior of 120bpm[22]. The symptoms include palpitations, lightheadedness, blurred vision, generalized weakness, fatigue, among others. The physiopathology of POTS combines multiple and coexistent mechanisms, such as autonomic denervation, hypovolemia and hyperadrenergic stimulation [23]. Although its etiology remains unclear, many studies had recently supported the hypothesis of it being an autoimmune disease[24]. The central argument for this hypothesis is the finding of autoantibodies in POTS patients' sera. These antibodies mainly target G-coupled proteins, including muscarinic, nicotinic and adrenergic receptors[24–27]. POTS was previously associated with small fiber neuropathy and, thus, may also be a part of ASIA syndrome. In Germany, C fiber involvement was observed in 45% of the 84 patients with POTS analyzed – and the reduced density of those fibers was correlated with a decreased adrenergic cardiac 123 I-metaiodobenzylguanidine (MIBG) uptake – suggesting an association between the small fiber neuropathy and the reduced myocardial postganglionic sympathetic innervation that could explain the abnormal tachycardia in those patients[28]. Other researchers looked for the correlation between

POTS and SFN. It was found that 20% of POTS patients' skin biopsy had signs of SFN[29].

e) *Similarities between Silicone Incompatibility Syndrome and ASIA syndrome following tattoo*

Recently, silicone breast implants were associated with the development of many general symptoms, for example, sleep disturbances, general fatigue, generalized pain, depression, hair loss, among others [9]. It has been proposed that those symptoms may relate to an autoimmune neurosensory dysautonomia, involving autoantibodies against G-protein coupled receptors of the autonomic nervous system such as the adrenergic and endothelin and angiotensin ones, which may result in small fiber neuropathy in a subgroup of these women [31]. Similarly, our patient had depression, anxiety and multiple neurologic complaints with an NCS-EMG showing decreased sympathetic response on her right foot, with no signs of large fiber polyneuropathy.

As for the above mentioned, autonomic-related manifestations (POTS, sicca syndrome, paresthesia and other signs of small fiber neuropathy) reported by our patient, we hypothesized the potential involvement of autoantibodies against GPCRs of the autonomic nervous system. These functional antibodies have already been described to be involved in the development of autoimmune diseases and other suspected immune- and dysautonomic-related disorders (such as Sjögren's syndrome, RA, SLE, MS, myasthenia gravis, POTS etc.[32–38]) and were found to be dysregulated in women with SBIs as well (Submitted/Personal communication). Indeed, we found increased circulation levels of anti-beta1, anti-beta2 and anti-M3 AAbs in our patient as compared to the normal ranges in healthy women, which might play a role in the appearance of autonomic-related symptoms in our patient.

f) *Potential therapies for ASIA syndrome following tattoo*

Some cases of ASIA syndrome had also been described following injection of S.C. methylmetacrylate [39–41]. Methylmetacrylate S.C. injections have been used in the last decades mainly with aesthetic goals in different body areas, from the lips to the buttocks. It has been recently proposed to treat those patients with intralesional neodymium laser [42]. Intralesional laser technique has been largely used as well for tattoo removal [43, 44]. As previously mentioned, frequently, in ASIA syndrome, the removal of the adjuvant exposure may ameliorate the signs and symptom of the disease. Extraction of silicone implants, for instance, was shown to improve the symptoms such as fatigue, arthralgia and sicca syndrome [45]. Hence, tattoo laser removal could be a potential treatment option for those patients.

### III. CONCLUSION

In this review, we raise the hypothesis of tattoo pigment as a new component of the group of adjuvants that trigger ASIA syndrome and question its safety in individuals genetically prone to develop autoimmunity. To reinforce our proposal, we described a 32-year-old woman with known Chron's disease that presented with arthralgia, morning stiffness, dry mouth and eyes, POTS and neurological complaints compatible with small fiber neuropathy after exposure to an extensive tattoo pigmentation (Fig 1-4). Although those symptoms had not been previously associated with the presence of tattoo ink, permanent tattoos had been previously linked to sarcoidosis and isolated uveitis [15, 46]. In addition, those symptoms have been related to other environmental exposures, such as to aluminium, other metals, silicone and vaccines [1, 6, 7, 9, 47]. In fact, some of the tattoo inks have been demonstrated to contain aluminum [30]. Moreover, removing the adjuvants had been shown to improve the clinical presentation and the laboratory markers in ASIA syndrome [9]. Tattoo removal with laser technique could be a potential solution for ASIA syndrome following tattoo.

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*Figures 1-4:* Images from our patient's extensive tattoos.

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## Teen Athlete with Recurrent Rhabdomyolysis: A Case Report

By Ana Cristina Fernandes, Inês Coelho, Marta Novo, Raquel Lima,  
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**Abstract- Background:** Rhabdomyolysis is a frequent disorder in the pediatric emergency room, and it can result from various acquired and inherited causes.

**Case presentation:** We report the case of a 15-year-old female triathlon athlete with recurrent exertional rhabdomyolysis. The clinical severity alerted for a subjacent cause, and further investigation was taken, leading to the diagnosis of very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.

**Conclusion:** Exertional rhabdomyolysis may be the first manifestation of a metabolic myopathy, like VLCAD deficiency. VLCAD deficiency has a broad clinical spectrum, and the most common is the late-onset, which presents mainly with episodic symptoms, with predominant muscular involvement and exercise-induced rhabdomyolysis.

**Keywords:** adolescent medicine, exertional rhabdomyolysis, sports medicine, metabolic myopathy, VLCAD deficiency.

**GJMR-F Classification:** NLMC Code: WE 168



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# Teen Athlete with Recurrent Rhabdomyolysis: A Case Report

Ana Cristina Fernandes <sup>α</sup>, Inês Coelho <sup>σ</sup>, Marta Novo <sup>ρ</sup>, Raquel Lima <sup>ω</sup>, Rita Pereira <sup>¥</sup> & Filipa Dias <sup>§</sup>

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## I. INTRODUCTION

Rhabdomyolysis is a relatively common condition, however the actual incidence of this clinical syndrome is unknown, and many mild cases probably go unrecognized. (1) This pathology is defined by elevated serum creatine kinase (CK) activity by at least ten times the normal range followed by a fast decline. It results from the rapid breakdown of skeletal muscle fibers, leading to leakage of potentially toxic cellular contents into the bloodstream. (2)

The leading causes for rhabdomyolysis are trauma, intense exercise, infection, drugs, and toxins, although it can result from a range of acquired and inherited causes. (3,4) Although many situations are self-limited and benign, the possibility of endocrine, metabolic, or neuromuscular disease should also be contemplated primary causes or contributing factors for the episode. (4)

The authors describe a case of a teen athlete with recurrent severe episodes of exertional rhabdomyolysis.

## II. CASE REPORT

A 15 year-old-girl, a triathlon athlete with daily trainings was admitted to the pediatric emergency room with a history of generalized myalgia and tea-colored urine following a triathlon training. She had an irrelevant family history with no consanguinity, had adequate weight and height, and a complete vaccination schedule for the age.

The patient revealed a similar episode one year before, following an intense effort, in which she didn't consult a doctor. The symptoms spontaneously resolved in 2 to 3 days. The patient denied consumption of drugs, fever, dysuria, asthenia, and other constitutional symptoms.

On examination, she had pale skin, dry tongue, tense, and swollen muscles of the upper and lower limbs with palpation-induced myalgia.

The blood diagnostic tests (Table 1) showed myoglobin >1.200 ng/L, creatine kinase (CK) > 85.340 IU/L, aspartate aminotransferase 4756 IU/L; alanine aminotransferase 564 IU/L; LDH >1.995 IU/L. Urinalysis showed false haematuria with no erythrocytes in the urine sediment. There were no changes in blood counts, infectious parameters, or kidney function.

The patient was admitted to the Pediatric Department to diagnose for exertional rhabdomyolysis and started aggressive hydration with intravenous fluids. She was hospitalized for five days with clinical and analytical (Table 2) improvement, being referenced for an out-patient follow-up.

During this follow-up, we realized that CK values decreased during the rest periods but increased to a thousand values after mild efforts (less intense training). She had no complaints suggestive of inflammatory myopathies. The endocrinological study was also negative.

In the course of the etiological investigation (Table 3), the metabolic study showed an acylcarnitine profile compatible with very-long-chain fatty acid acyl-CoA dehydrogenase (VLCAD) deficiency. The genetic analysis confirmed the findings, identifying the variants p.Gly140Glu (c.419>A) and p.Gly442Ala (c.1322G>C) in heterozygosity in *acyl-CoA dehydrogenase, very long-chain* (ACADVL) gene. Thus, establishing the diagnosis of VLCAD.

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### III. DISCUSSION

Exertional rhabdomyolysis (ER) happens in reaction to excessive, prolonged, repetitive exercise, or normal exercise under extreme circumstances. Well described among athletes, it is presented by severe muscle pain, muscle swelling and muscular weakness within 24h to 72h after the exercise, and can be associated with myoglobinuria.(5)

When assessing a patient diagnosed with rhabdomyolysis, it is essential to obtain a thorough history regarding the onset, location, quality of the muscle discomfort, and the temporal relationship to metabolically stressful triggers such as strenuous activity, fasting, fever, infection, cold exposure, and medications. Physicians should question about altered urine coloration, previous similar episodes, and if any family members are similarly affected. As many metabolic myopathies have an autosomal recessive inheritance, consanguinity in the family should be stated.(3)

Even though the ER frequently represents a 'physiological' response to extreme physical exercise, the physician should be aware of the characteristics that may alert for an underlying cause. (6)Some of those clinical indicators are female patients; recurrent episodes of exertional rhabdomyolysis; persistent elevation of CK or weakness four weeks after the event; rhabdomyolysis in the course of regular exercise; CK more than fifty times the upper limit of normal range; family history of similar episodes.(2,6,7)

In these circumstances, the differential diagnosis must consider metabolic myopathies, heterogeneous group of genetically defined syndromes that may appear at any age. They characterized by defects in the biochemical pathways of storage, mobilization, and utilization of the substrates of muscle energy production. A detailed clinical approach will help distinguish between the three major disorders (glycogenosis, lipid-related disorders, or mitochondrial diseases).(8,9) The most important energy source of the muscle depends on the intensity and duration of the exercise, which can provide clues to the specific condition. Fatty acids are the primary energy source at rest, when fasting, or during endurance activities.(3)

Very long-chain acyl-CoA dehydrogenase (VLCAD) catalyzes the first step of the fatty acid  $\beta$ -oxidation spiral, and its deficiency results in the reduced capacity to utilize fat. Depending on the severity of the enzymatic deficiency and other individual factors there is a continuum of clinical severity of VLCAD deficiency, divided into three phenotypes. The severest form with early-onset cardiac and multiorgan failure typically arrives in the first months of life with hypertrophic or dilated cardiomyopathy, pericardial effusion, and arrhythmias, as well as hypotonia, hepatomegaly, and intermittent hypoglycemia. An infantile form with

hypoketotic hypoglycemia and hepatomegaly, but without cardiomyopathy, is typically presented during early childhood. The most common form is the late-onset and milder type that poses with intermittent rhabdomyolysis provoked by exercise with or without myoglobinuria, muscle cramps and pain, and exercise intolerance. Cardiomyopathy and liver dysfunction do not usually appear in late-onset VLCAD deficiency. (8,10-12)

VLCAD deficiency is the second most common disorder of fatty acid oxidation in Europe and shows an autosomal recessive inheritance pattern. (13)The diagnosis is based on the assessment of a metabolic profile, indicating abnormal elevation of long-chain acylcarnitine.(14)It also can be performed by other methods, including molecular analysis (which may be inconclusive in cases of novel mutations or genetic variants), enzyme testing in fibroblasts and lymphocytes as well as flux studies in fibroblasts. (13)The genetic basis is complex, caused by a variety of pathogenic variants in the *ACADVL* gene, the most common of which is c.848T>C (p.V283A), which retains 11-12% residual enzymatic activity in homozygotes.(11) The inheritance is recessive autosomal, with homozygous or compound heterozygous mutations.(12)

In general, treatment aims to prevent acute episodes. Regular, frequent meals rich in carbohydrates and low in long-chain fats is advised. Medium-chain triglycerides may also be helpful. (3) It is imperative to notice that rhabdomyolysis is a significant complication in VLCAD deficiency that may lead to kidney damage and even renal failure and can be triggered by prolonged or intense exercise, prolonged fasting, and fever or illness. (15)

The prognosis of the late-onset form is usually good, but the outcome isn't completely obvious, so careful management is desirable. (10)

### IV. CONCLUSION

Exertional rhabdomyolysis may be the first expression of a genetic muscle disease that which lowers the exercise threshold for developing muscle breakdown. (6)

The patient presented was a teen athlete accustomed to regular high intensity exercise with no complaints of effort intolerance.

Nonetheless, the severely elevated CK and the history of recurrent rhabdomyolysis took us to the clue of a subjacent cause and guided the ambulatory work-up.

Although this case report stated a typical clinical presentation, the differential diagnosis of severe rhabdomyolysis is broad, and a high suspicion is needed to undergo further investigation.

The identification of an underlying genetic disorder is essential for acute management and, most importantly for subsequent counselling.

The identification of an underlying genetic disorder is essential for acute management and, most importantly for subsequent counselling.

On the genetic analysis, the variants p.Gly140Glu (c.419>A) and p.Gly442Ala (c.1322G>C)

were identified, the first not yet described in the literature and the second without obvious pathogenicity. Bioinformatics predictors of these variants are suggestive of pathogenicity.

**Tabela 1:** Diagnostic tests at the pediatric emergency room

Hemoglobin (g/L)	147
White blood cell and differential count (x10 <sup>9</sup> /L)	
Leukocytes	13.6
Neutrophils	11.6
Lymphocytes	1.2
Monocytes	0.8
Eosinophils	0.0
Basophils	0.1
Platelets (x10 <sup>9</sup> /L)	334
Prothrombin time (sec)	15.2
aPTT (sec)	26.1
Myoglobin (ng/L)	>1200
Glucose (mg/dL)	84
Aspartate transaminase (AST) (U/L)	4756
Alanine transaminase (ALT) (U/L)	564
Creatine kinase (CK) (IU/L)	>85340
Lactic Acid Dehydrogenase (LDH) (U/L)	>1995
Na <sup>+</sup> (mmol/L)	137
K <sup>+</sup> (mmol/L)	4.3
Cl <sup>-</sup> (mmol/L)	107
Ca <sup>2+</sup> (mg/dL)	8.6
P (mg/dL)	5.1
Blood urea nitrogen (BUN) (mg/dL)	22
Creatinine (mg/dL)	0.7
C-Reactive Protein (CRP) (mg/dL)	18
Urinalysis	+++ Blood

**Tabela 2:** Evolution during hospitalization

	Day1	Day 2	Day 3	Day 4	Day 5
AST (U/L)	4756	5364	4633	-	1222
ALT (U/L)	564	888	1234	-	899
CK (U/L)	>85340	16046	49054	19446	8939
BUN (mg/dL)	22	12	10	9	8
Creatinine (mg/dL)	0.7	0.7	0.5	0.6	0.5

**Tabela 3:** Etiological investigation

Thyroid-Stimulating Hormone (TSH) (μIU/mL)	1.17
Uric Acid (mg/dL)	2.9
Erythrocyte sedimentation rate (mm/h)	8
Haptoglobin (mg/dL)	93
Angiotensin Converting Enzyme (U/L)	416
C3 (g/L)	1.08
C4 (g/L)	0.254
ANA	Negative
dsDNA	Negative
Thyroglobulin Antibody	Negative
Thyroid peroxidase	Negative
Metabolic study for GLUT diseases	Negative
Global metabolic study	Acylcarnitine deficiency in very long-chain fatty acid dehydrogenase



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Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

Career

Credibility

Financial

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Exclusive



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Exclusive

Financial

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Financial

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ASSOCIATE	FELLOW	RESEARCH GROUP	BASIC
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<b>Certificate</b> , LoR and Momento 2 discounted publishing/year <b>Gradation</b> of Research 10 research contacts/day 1 GB Cloud Storage GJ Community Access	<b>Certificate</b> , LoR and Momento <b>Unlimited</b> discounted publishing/year <b>Gradation</b> of Research <b>Unlimited</b> research contacts/day 5 GB Cloud Storage <b>Online Presense</b> Assistance GJ Community Access	<b>Certificates</b> , LoRs and Momentos <b>Unlimited</b> free publishing/year <b>Gradation</b> of Research <b>Unlimited</b> research contacts/day <b>Unlimited</b> Cloud Storage <b>Online Presense</b> Assistance GJ Community Access	GJ Community Access



# PREFERRED AUTHOR GUIDELINES

## **We accept the manuscript submissions in any standard (generic) format.**

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from <https://globaljournals.org/Template>

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at [submit@globaljournals.org](mailto:submit@globaljournals.org) or get in touch with [chiefeditor@globaljournals.org](mailto:chiefeditor@globaljournals.org) if they wish to send the abstract before submission.

## BEFORE AND DURING SUBMISSION

Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and *agree to Global Journals' ethics and code of conduct*, along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

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It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

## POLICY ON PLAGIARISM

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures



- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

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1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

### Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

### Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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## PREPARING YOUR MANUSCRIPT

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.



### ***Manuscript Style Instruction (Optional)***

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

### ***Structure and Format of Manuscript***

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
- k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



## FORMAT STRUCTURE

***It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.***

All manuscripts submitted to Global Journals should include:

### **Title**

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

### **Author details**

The full postal address of any related author(s) must be specified.

### **Abstract**

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

### **Keywords**

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, "What words would a source have to include to be truly valuable in a research paper?" Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

### **Numerical Methods**

Numerical methods used should be transparent and, where appropriate, supported by references.

### **Abbreviations**

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

### **Formulas and equations**

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

### **Tables, Figures, and Figure Legends**

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.





## Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

### PREPARATION OF ELETRONIC FIGURES FOR PUBLICATION

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

### TIPS FOR WRITING A GOOD QUALITY MEDICAL RESEARCH PAPER

**1. Choosing the topic:** In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

**2. Think like evaluators:** If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

**3. Ask your guides:** If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

**4. Use of computer is recommended:** As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

**5. Use the internet for help:** An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



**6. Bookmarks are useful:** When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

**7. Revise what you wrote:** When you write anything, always read it, summarize it, and then finalize it.

**8. Make every effort:** Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

**9. Produce good diagrams of your own:** Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

**10. Use proper verb tense:** Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

**11. Pick a good study spot:** Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

**12. Know what you know:** Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

**13. Use good grammar:** Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

**14. Arrangement of information:** Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

**15. Never start at the last minute:** Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

**16. Multitasking in research is not good:** Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

**17. Never copy others' work:** Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

**18. Go to seminars:** Attend seminars if the topic is relevant to your research area. Utilize all your resources.

**19. Refresh your mind after intervals:** Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.



**20. Think technically:** Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

**21. Adding unnecessary information:** Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

**22. Report concluded results:** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

**23. Upon conclusion:** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

## INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

### Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

### Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

*The introduction:* This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

### The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

### General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

**To make a paper clear:** Adhere to recommended page limits.



### *Mistakes to avoid:*

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

### **Title page:**

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

**Abstract:** This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

*Reason for writing the article—theory, overall issue, purpose.*

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

### **Approach:**

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

### **Introduction:**

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



*The following approach can create a valuable beginning:*

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

#### **Approach:**

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

#### **Procedures (methods and materials):**

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

#### **Materials:**

*Materials may be reported in part of a section or else they may be recognized along with your measures.*

#### **Methods:**

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

#### **Approach:**

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

#### **What to keep away from:**

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.





**Results:**

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

**Content:**

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

**What to stay away from:**

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

**Approach:**

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

**Figures and tables:**

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Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

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- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
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- Recommendations for detailed papers will offer supplementary suggestions.

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<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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