A model-based approach to improve intranasal sprays for respiratory viral infections

Saikat Basu^{1,*}, Mohammad Mehedi Hasan Akash¹, Yueying Lao², Pallavi
 A Balivada², Phoebe Ato², Nogaye K Ka², Austin Mituniewicz³, Zachary
 Silfen², Julie Suman⁴, Arijit Chakravarty⁵, Diane Joseph-McCarthy^{2,6}

- ¹ Department of Mechanical Engineering, South Dakota State University, Brookings, SD 57007, United States
 - ² Department of Biomedical Engineering, Boston University, MA 02215, United States
- ³ Joint Department of Biomedical Engineering, University of North Carolina North Carolina State University, Chapel Hill, NC 27599, United States
- 4 Next Breath an Aptar Pharma Company, Baltimore, MD 21227, United States
- ⁵ Fractal Therapeutics, Cambridge, MA 02319, United States
- ⁶ Bioengineering Technology and Entrepreneurship Center, Boston University, MA
 02215, United States
- 16 E-mail: * Saikat.Basu@sdstate.edu

Abstract. Drug delivery for viral respiratory infections, such as SARS-CoV-2, can 17 be enhanced significantly by targeting the nasopharynx, which is the dominant initial 18 infection site in the upper airway, for example by nasal sprays. However, under the 19 standard recommended spray usage protocol ("Current Use", or CU), the nozzle enters 20 the nose almost vertically, resulting in sub-optimal deposition of drug droplets at the 21 nasopharynx. Using computational fluid dynamics simulations in two anatomic nasal 22 geometries, along with experimental validation of the generic findings in a different 23 third subject, we have identified a new "Improved Use" (or, IU) spray protocol. It 24 entails pointing the spray bottle at a shallower angle (almost horizontally), aiming 25 slightly toward the cheeks. We have simulated the performance of this protocol for 26 conically injected spray droplet sizes of $1 - 24 \mu m$, at two breathing rates: 15 and 27 30 L/min. The lower flowrate corresponds to resting breathing and follows a viscous-28 laminar model; the higher rate, standing in for moderate breathing conditions, is 29 turbulent and is tracked via Large Eddy Simulation. The results show that (a) droplets 30 sized between $\sim 6-14 \ \mu m$ are most efficient at direct landing over the nasopharyngeal 31 viral infection hot-spot; and (b) targeted drug delivery via IU outperforms CU by 32 approximately 2 orders-of-magnitude, under the two tested inhalation conditions. Also 33 quite importantly, the improved delivery strategy, facilitated by the IU protocol, is 34 found to be robust to small perturbations in spray direction, underlining the practical 35 utility of this simple change in nasal spray administration protocol. 36

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(249 words)

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40 1. Introduction

The global respiratory pandemic¹ caused by the severe acute respiratory syndrome 41 coronavirus 2 (SARS-CoV-2) has thrust the field of fluid mechanics back into public 42 eve, perhaps for the first time since the era of 1960s' space race.² Flow physics plays an 43 essential role in almost every aspect of respiratory viral infections; none the more so than 44 in targeted delivery of drugs to the infection hot-spots along the airway. Upper airway 45 sites, in specific the ciliated epithelial cells that line the back of the nasal cavity at the 46 nasopharynx (see Fig. 1) and are rich in angiotensin-converting enzyme 2 (ACE2) surface 47 receptors, have been marked out^{3-5} as the trigger zones for infection onset owing to 48 SARS-like airborne viral respiratory pathogens. An early intervention method that can 49 target the initial dominant infection site, i.e. the nasopharynx, is hence imperative for 50 limiting asymptomatic transmission of the exhaled pathogenic particulates as well as for 51 preventing systemic lower airway progression of the disease in a host, aggravating toward 52 severe illness.^{6,7} Of critical interest here, based on the brisk pace at which lower airway 53 infections ensue after the emergence of initial symptoms, it has been conjectured^{3,8,9} 54 that the nasopharynx also acts as the seeding zone for spread of the disease to the lungs 55 via lower airway aspiration of virus-laden boluses of nasopharyngeal fluids. Another 56



Figure 1: Panels (a) - (c) respectively show the axial, sagittal, and coronal views of the computed tomography (CT) based upper airway reconstruction in Subject 1. Panels (d) - (f) depict representative CT slices for the same subject. Therein, the green lines in (d) and (e) correspond to the location of the sagittal section shown in (f); the orange lines in (d) and (f) correspond to the location of the coronal section shown in (e); the red lines in (e) and (f) correspond to the location of the axial section shown in (d). Panels (g) - (i) respectively show the axial, sagittal, and coronal views of the CT-based upper airway reconstruction in Subject 2. Panels (j) - (l) depict representative CT slices for the same subject. Therein, the green lines in (j) and (k) correspond to the location of the sagittal section shown in (l); the orange lines in (j) and (l) correspond to the location shown in (k); the red lines in (k) and (l) correspond to the location of the axial section shown in (j). The nasopharynx has been marked in blue in panels (a) - (c) and (g) - (i).

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⁵⁷ concern is the mutation rate of SARS-CoV-2 and how the nature of the fitness landscape
⁵⁸ renders the virus amenable to evolving, potentially resulting in more virulent strains.¹⁰
⁵⁹ A nasal spray – that can administer nasal hygiene products, prophylactics, and antiviral
⁶⁰ agents – would address these concerns if it can efficiently deliver the pharmaceutics at
⁶¹ the virus-affected upper airway sites, thereby reducing the risk of viral droplet/aerosol
⁶² shedding as well as mutation within the host.

While the nasal sprays do provide a simple, yet robust, drug delivery modality, especially during the infection onset phase of respiratory viruses; the choice still comes with at least two key open questions, *viz.* (a) what are the intranasally sprayed drug droplet sizes that would maximize targeted delivery at the initial dominant infection site, the nasopharynx?; and (b) is there a way to revise the nasal spray usage protocols, to enhance the delivery of drugs at the infected site?

This study addresses the above questions through implementing experimentally-69 validated computational fluid dynamics (CFD) modeling of the respiratory transport 70 process in computed tomography (CT)-based anatomically realistic upper airway 71 geometries. The related simulations replicate sprayed drug transmission against two 72 different ambient inhalation rates, viz. 15 and 30 L/min; standing in respectively for 73 relaxed and moderate steady breathing conditions.¹¹ Preliminary findings pertaining 74 to this work have been presented at the American Physical Society's Division of Fluid 75 Dynamics Annual Meeting 2021.¹² 76

77 2. Materials and methods

78 2.1. Anatomic upper airway reconstruction

The *in silico* upper airway geometries used here were reconstructed from the de-identified medical-grade CT imaging data derived from two healthy test subjects. Subject 1 was a Caucasian female in the age range 61-65 years; Subject 2 was a Caucasian female in the age range 36-40 years. Use of the archived and anonymized medical records was approved with exempt status by the Institutional Review Board (IRB) for the University of North Carolina (UNC) at Chapel Hill, with informed consent waived for retrospective use in computational research.

In terms of imaging resolution, the 86 CT slices of the airway cavities were ex-87 tracted at coronal depth increments of 88 0.348 mm in Subject 1's scans and 0.391 89 mm in Subject 2's scans. Digitization of 90 the anatomic airspaces was carried out 91 on the image processing software Mimics 92 Research v18.0 (Materialise, Plymouth, 93 Michigan), using a radio-density delina۵ eation range of -1024 to -300 Hounsfield 95



Figure 2: The schematic shows the two tested nasal spray usage protocols, *viz.* "Current Use" (or CU, represented by the dashed line) and "Improved Use" (or IU, represented by the solid line). Cartoon illustration is by the Dr. Ferrer Biopharma (Hallandale Beach, FL) graphics design team.

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Figure 3: Spatial differences between the Current Use (CU) and Improved Use (IU) spray placement protocols, as visible sagittally in Subject 1. Nasopharynx is marked in blue.

units, and was complemented by clinically-monitored hand-editing of the selected pix-96 els to ensure anatomic accuracy. The output STL (stereolithography) geometries were 97 then spatially meshed on ICEM-CFD 2019 R3 (ANSYS Inc., Canonsburg, Pennsyl-98 vania) with minute volume elements. Therein to confirm grid-independent solutions, 99 established mesh-refinement protocols^{13,14} were followed such that each computational 100 grid contained more than 4 million unstructured, graded, tetrahedral elements. To en-101 able accurate tracking near tissue surfaces, further mesh refinement involved adding 102 three prism layers at the cavity walls, with 0.1-mm thickness and a height ratio of 1. 103

2.2. Simulation of breathing transport and drug delivery 104

Inhalation parameters for gentle-to-moderate breathing conditions were numerically 105 replicated at 15 and 30 L/min.¹¹ The lower flow rate commensurate with resting 106 breathing is dominated by viscous-laminar steady-state flow physics.^{15–20} The higher 107 flow rates however trigger shear-induced 21-23 flow separation from the tortuous cavity 108 walls, resulting in turbulence,^{24–27} which was tracked through Large Eddy Simulation 109 (LES), with sub-grid scale Kinetic Energy Transport Model²⁸ accounting for the 110 The computational scheme on ANSYS Fluent 2019 R3 small-scale fluctuations. 111 employed a segregated solver, with SIMPLEC pressure-velocity coupling and second-112 order upwind spatial discretization. Solution convergence was monitored by minimizing 113 mass continuity and velocity component residuals, and through stabilizing mass flow 114 rate and static pressure at airflow outlets (see the nasopharyngeal outlet location in 115 Fig. 1). For the pressure gradient-driven laminar airflow solutions, the typical execution 116



Figure 4: Spatial differences between the Current Use (CU) and Improved Use (IU) spray placement protocols, as visible sagittally in Subject 2. Nasopharynx is marked in blue.

time for 5000 iterations was 2–3 hours with 4-processor based parallel computations operating at 3.1 GHz speed on Xeon nodes. Additionally, the LES computations each required a run-time of 1–2 days, for a pressure-driven simulated flow interval of 0.25 s, with a time-step of 0.0001 s. To realistically capture the inhaled warmed-up air transport along the respiratory pathway, its density and dynamic viscosity were set at 1.204 kg/m^3 and $1.825 \times 10^{-5} \text{ kg/m.s}$, respectively.

Spray dynamics against the ambient airflow was tracked via Lagrangian-based 123 inert discrete phase simulations with a Runge-Kutta solver, with localized droplet 124 clustering along intranasal tissues obtained through numerically integrating the 125 transport equations that consider airflow drag, gravity, and other body forces relevant 126 for small particulates, e.g., the Saffman lift force, and by implementing a no-slip trap 127 boundary condition on the cavity walls. Note that Brownian effects were neglected in 128 view of the tracked droplet sizes. The drug formulation density was set to 1.5 g/ml. All 129 simulations released monodispersed inert drug droplets ranging in diameters from 1-24130 μ m, with 3000 monodispersed inert droplets being released during each iteration. The 131 droplets were injected into the airspace from a single source point where the spray nozzle 132 is located, streaming out in a hollow-cone shape, mimicking the action of a nasal spray; 133 this method of release is referred to as a cone injection. The Valois VP7, an affordable 134 mass-produced pharmaceutical nasal spray pump, with its accompanying dimension 135 properties, such as plume angle and initial spray velocity, was used as an initial point 136 of reference for the cone injections.²⁹ The droplets were given an initial velocity of 10 137

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 m/s^{30} and a total flow rate of 1×10^{-20} kg/s. The plume angle and insertion depth were selected¹⁵ to be 27.93° and 5 mm, respectively; by varying the spray direction – an optimal usage condition that augments droplet deposition at the target site was identified. See our earlier publications^{5,15} for additional details on the numerical setup.

142 2.3. On how to hold the spray bottle

A key parameter for targeted delivery is the direction of the nasal spray axis, as 143 the sprayed droplet trajectories are often inertia-dominated.^{15,18,31,32} Instructional 144 ambiguities^{33,34} point toward a lack of definitive knowledge on the best ways to 145 use a nasal spray device, with different commercial sprayers often offering somewhat 146 contrasting recommendations. There is, however, a consensus that the patient should 147 tilt her/his head slightly forward, while holding the spray bottle upright.^{33,35} There 148 is an additional clinical recommendation to avoid pointing the spray directly at the 149 septum, which is the separating cartilaginous wall between the two sides of the nasal 150 cavity. These suggestions were adopted in our standardization^{15,36} of "Current Use" 151 (CU) protocol for topical sprays. The digital models were inclined forward by an angle 152 of 22.5°, and the vertically-placed upright³³ spray axis was aligned closer to the lateral 153 nasal wall, at one-third of the distance between the lateral side and septal wall. Finally, 154 the spray bottle was placed at the nostril to penetrate 5-mm into the airspace, to conform 155 with the package recommendations of commercial sprayers³⁵ for a "shallow" intranasal 156 nozzle placement. 157

While the CU protocol would provide the acceptable state-of-art for targeted drug 158 delivery with nasal sprayers, the key focus of this study was to perturb that spray 159 direction to test alternate protocols that bear the promise to improve delivery of drugs 160 at the nasopharyngeal infection site. Our earlier findings¹⁵ showed that to target the 161 clinical site of ostiomeatal complex, or OMC (a key target site for corticosteroid-based 162 topical therapeutic management for chronic rhinosinusitis^{15,19} and allergic rhinitis³⁷), 163 the spray axis should be oriented to pass through the OMC itself. The inertial motion of 164 the spraved particulates assists such transport mechanism. Taking cue, to optimize the 165 spray administration protocol in the current study, we oriented the nozzle such that the 166 spray axis passes through the nasopharynx, and have named the strategy as "Improved 167 Use", or IU protocol. When determining the IU direction, it was important to satisfy 168 three conditions as a way of ensuring the optimal placement of a nasal spray for drug 169 release: (i) the extended spray axis for the IU protocol must intersect the nasopharynx; 170 (ii) the spray axis must not cut through the septal wall; and (iii) the axis should intersect 171 the lateral wall in the posterior part of the nasal cavity. See the cartoonized Fig. 2 for 172 a broad-spectrum visual difference between the presently recommended CU and the 173 to-be-tested IU protocols. Additionally, Figs. 3 and 4 depict the spatial distinctions in 174 spray placement between the IU and CU protocols, in the two test subjects, as visible 175 from the sagittal perspective. 176

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177 2.4. Tolerance sensitivity analysis

Once the IU for an airway reconstruction was determined (following guidelines described in Section 2.3), a tolerance sensitivity study was performed to assess how far the user could deviate from the determined IU spray direction and still get similar regional drug deposition results, or in other words how robust (or, on the contrary, user-sensitive) the chosen IU direction really is.

To generate the new perturbed axes in the *in silico* space, a 1-mm radius circle 183 was created perpendicular to the perturbed direction either 5-mm or 10-mm away from 184 the central point on the nostril plane of each model. The two different distances were 185 chosen in order to test the sensitivity of the results to different perturbation trends. 186 The 5-mm method was performed on the left nostril of the subjects, while the 10-187 mm method was performed on the right nostril. Five peripheral points equidistant 188 from each other were then selected on the circle created. The axis formed between the 189 centroid point on the nostril plane and the peripheral point on the circle determined 190 the new perturbed direction. In all, five additional perturbed spray axes were created, 191 henceforth referred to as PD 1-5. For each new perturbed direction, the injection 192 point was selected by measuring 5-mm from the centroid on the nostril plane, toward 193 the nasopharynx. This was performed for both the left and right nostrils of Subjects 194 1 and 2. Each new identified PD axis was evaluated using the criteria developed to 195 identify the IU direction, and drug delivery simulations were performed following the 196 methods described in Section 2.2. The results of the tolerance simulations were analyzed 197 for congruity using Pearson's correlation coefficient. 198

199 2.5. Experimental validation of computationally predicted spray performance

To extract a sense of real spray performance that could be projected from the in 200 silico framework, we linked the computationally predicted nasopharyngeal droplet 201 deposition efficiencies with the size distribution of droplets (see Fig. 5) in two 202 actual over-the-counter spray products: FlonaseTM (Fluticasone Propionate) and 203 NasacortTM (Triamcinolone Acetonide). Both are commonly prescribed medications 204 and are commercially available. Four units of each product were tested at Next Breath, 205 an Aptar Pharma company (Baltimore, MD, USA). The team measured the plume 206 geometry through a SprayVIEW[®] NOSP, which is a non-impaction laser sheet-based 207 instrument. With the droplet sizes in a spray shot following a log-normal distribution, 208 the droplet size distribution (where droplet diameters are represented by x) can be 209 framed as a probability density function:³⁸ 210

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$$f(x) = \frac{1}{\sqrt{2\pi}x\ln\sigma_g} \exp\left[-\frac{(\ln x - \ln x_{50})^2}{2(\ln\sigma_g)^2}\right].$$
 (1)

Here the mass median diameters (alternatively, the geometric mean diameter³²) for FlonaseTM and NasacortTM were respectively, $x_{50} = 37.16 \ \mu\text{m}$ and $43.81 \ \mu\text{m}$; the corresponding geometric standard deviations were respectively, $\sigma_q = 2.080$ and 1.994.

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The latter quantifies the span of the droplet size data. Note that the measurements were also collected with and without a saline additive in the sprayer, with the tests returning similar droplet size distributions. The reader is referred to our previous publications^{15, 18} for additional details.

To test the validity and extensibility 219 of the computational predictions derived 220 for real sprays, we subsequently performed 221 multiple runs of physical spray experi-222 ments with 10-ml boluses (for measurable 223 posterior deposits) of watery solutions in-224 jected through a 3D-printed anatomically 225 realistic airway cavity of a different sub-226 ject, Subject 3 (a Caucasian male belong-227 ing to the age range 41-45 years; use of the 228 subject's de-identified imaging data with 229 CT-slice resolution of 0.352 mm was ap-230 proved with exempt status by the UNC 231 Chapel Hill IRB for retrospective use). 232 Printing of the related anterior soft plastic 233 part on a Connex3TM 3D printer was car-234 ried out using polymer ink-jetting process 235 on Tangogray FLX950 material, approxi-236



Figure 5: Measured distribution of droplet sizes in 1-mg sprayed mass from over-the-counter FlonaseTM (Fluticasone Propionate) and NasacortTM (Triamcinolone Acetonide) spray products, over the test size range of ~ 1 - 24 μ m used for *in silico* tracking. Note that rigorous testing for droplets > 24 μ m clearly show⁵ that they would deposit along the anterior nasal cavity and will not directly land at the posterior target site of nasopharynx.

mately mimicking the material properties of the external nares and the internal tissues and cartilages. The 3D-printed cavity extent terminated just before the nasopharynx, thereby allowing us to measure the outflow volume of administered solution reaching nasopharyngeal walls. See the last visual under results for a pictorial representation of the 3D-printed soft nose used in the experiments.

242 3. Results

243 3.1. Optimal direction of spray axis and droplet sizes for effective targeting

Airflow and droplet tracking was simulated for spray nozzle placement in the left and 244 right nasal airways of Subjects 1 and 2 under two standard inhalation rates (15 and 30 245 L/min), for drug droplet diameters $1 - 24 \mu m$, and for the two spray directions as per 246 the CU and IU protocols. In all eight cases, the IU direction of the spray axis results in 247 higher deposition at the nasopharynx in comparison to the CU protocol over a defined 248 range of particle sizes (see Fig. 6). For instance: if we examine the deposition trends 249 for spray administration through the right nostril of Subject 2 for the laminar regime 250 inhalation (i.e. at 15 L/min), the peak nasopharyngeal deposition for IU is 46.5% for 251 13 μ m drug droplets (Fig. 6(b)), while the peak deposition for CU is only 0.53% for 252 14 μ m drug droplets (see again Fig. 6(b) and the corresponding zoomed-in for the CU 253



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Figure 6: Panels (a) – (d) show the comparison of the regional deposition trends at the nasopharynx of Subject 1, for the IU and CU protocols, with monodispersed conical injections. The rows (a) – (b) are for 15 L/min inhalation; rows (c) – (d) are for 30 L/min inhalation. Panels (e) – (f) depict the representative zoomed-in trends for nasopharyngeal deposition with the CU protocol, on administering the spray through the right nostril. Similarly, panels (g) – (j) show the comparison of the regional deposition trends at the nasopharynx of Subject 2, for the IU and CU protocols. The rows (g) – (h) are for 15 L/min inhalation; rows (i) – (j) are for 30 L/min inhalation. Panels (k) – (l) depict the representative zoomed-in trends for nasopharyngeal deposition with the CU protocol, on administering the spray through the right nostril. The IU trend lines are marked in red; the CU trend lines are in blue. The reader should note the abbreviated vertical range on the (e) – (f) and (k) – (l) plots, prompted by the 2 orders-of-magnitude smaller deposition efficiency with CU.

delivery trends visual in Fig. 6(k)). In general, the droplet size range of $\sim 6 - 14 \ \mu m$ is found conducive to targeted nasopharyngeal delivery with the IU protocol, considering a 2% cut-off for deposition efficiency of the tracked monodispersed droplet cluster of each size . The nearly hundred-fold increase in targeted deposition is remarkable and is achievable simply by re-orienting the spray axis from CU to IU.



Figure 7: Panels (a) and (b) illustrate the *in silico* detection of the perturbed spray directions (PD), deviating slightly from the IU axis. The direction vectors are from the centroid of the nostril plane to the points lying on a 1-mm circle that is 5 mm and 10 mm (respectively for the left and right nostril placement) from the nostril plane centroid (see Section 2.4 for associated details). Panels (c) – (f) for Subject 1 and panels (g) – (j) for Subject 2 compare the respective nasopharyngeal deposition trends for PD 1 – 5 directions, with respect to that of the "Improved Use" (IU) protocol. The top row is for 15 L/min inhalation; the bottom row is for 30 L/min inhalation rate. Clustering of the plots signifies robustness of the IU usage parameters; in other words, the IU protocol is satisfactorily less sensitive to user subjectivities.

259 3.2. Assessing sensitivity to IU perturbations

The variation of the nasopharyngeal deposition percentages over the assessed droplet size 260 range $(1 - 24 \ \mu m)$ was compared between that of the IU protocol and for each of the PD 261 1-5 cases. Pearson's correlation coefficient was greater than 0.5 for nearly every such 262 comparison (see Fig. 7 and Table 1), showing a high degree of linearity between the new 263 perturbed directions and the IU protocol. Moreover, the p-value associated with each 264 correlation was much lower than the significance level, i.e. 0.05. This indicates that there 265 is a statistically significant correlation between the simulation results on the targeted 266 nasopharyngeal drug delivery for the IU and the perturbed directions. Physically, the 267 satisfactory correlation between IU and PD 1-5 establishes the robustness of the IU 268 spray protocol to user subjectivities. 269

270 3.3. Verification of optimal droplet sizes through scaling analysis

The droplet size ranges that registered peak nasopharyngeal deposition under each inhalation condition were further analyzed and validated for reliability, through a Stokes

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 $_{273}$ number-based scaling analysis.³⁹ The Stokes number (St) is defined as³²

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$$=\frac{U\,\rho_{\mathbb{D}}\,\mathbb{D}^2\,C_c}{18\,\mu\,d},\tag{2}$$

where U for the present system is the airflow rate divided by flux area, $\rho_{\mathbb{D}}$ is the material density of the inhaled droplets, C_c is the Cunningham slip correction factor, μ is the dynamic viscosity of the ambient medium i.e. air, and d represents the characteristic diameter of the flux cross-section. Now, all other flow and morphological parameters staying invariant, Equation 2 directly leads to the following scaling law:

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$$\frac{\mathbb{D}_2}{\mathbb{D}_1} = \sqrt{\frac{Q_1}{Q_2}}.$$
(3)

Herein (Q_i, \mathbb{D}_i) are different airflow rate and droplet size pairings. Let us now consider 281 a representative example, say the right nostril spray administration in Subject 2. For 282 at least 2% nasopharyngeal deposition, the computationally predicted ideal droplet size 283 range during 30 L/min inhalation is $[\mathbb{D}_{\min}, \mathbb{D}_{\max}] = [5, 11] \mu m$. Equation 3 can 284 consequently help us to project the corresponding ideal size range at the lower inhalation 285 rate of 15 L/min. If the to-be-projected droplet size range that would generate peak 286 nasopharyngeal deposition during the latter case is represented by $[\mathbb{D}'_{\min}, \mathbb{D}'_{\max}]$ in μ m, 287 then 288

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$$\frac{\mathbb{D}'_{\min}}{5} = \frac{\mathbb{D}'_{\max}}{11} = \sqrt{\frac{30}{15}}.$$
(4)

This results in $\mathbb{D}'_{\min} = 7.07 \ \mu$ and $\mathbb{D}'_{\max} = 15.56 \ \mu$. Despite the simplicity of this 290 scaling analysis, the computationally identified range $9-24 \ \mu m$ for the same breathing 291 conditions hence follows the same trend on the number scale, in terms of the respective 292 variations from the extremal limits of $[\mathbb{D}_{\min}, \mathbb{D}_{\max}]$. The penultimate panel in Fig. 8 293 visually illustrates this specific example; see the remaining panels in Fig. 8 for all the 294 other test cases. The directional change of the extremal limits for the St-projected ideal 295 droplet size ranges remarkably agrees with the corresponding CFD-based size ranges in 296 all cases, except in one trivial outlier: see panel (c) for Subject 1's right nostril, there 297 the maximum ideal size limits for both 15 and 30 L/min are 24 μ m; the St-projected 298 maximum ideal droplet size for 30 L/min is, however, 33.94 μ m. 299

300 3.4. Comparison of the in silico findings to physical experiments

Panel (a) in Fig. 9 portrays the order-of-magnitude improvement in targeted drug 301 deposition at the nasopharynx (with the IU protocol over the CU protocol), when 302 taking into the account the droplet size distributions^{15,18} in real over-the-counter spray 303 products, viz. FlonaseTM and NasacortTM, in an administered shot. See Section 2.5 304 for the related study methods. Considering all the test cases, the average IU-over-CU 305 improvement for the two chosen spray products, as projected from the CFD simulations, 306 was 2.117 orders-of-magnitude with a standard deviation of 0.506 orders. The physical 307 experiments in Subject 3 (presenting an entirely different anatomy) show a comparable 308

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Figure 8: Panels (a) – (d) for Subject 1 and panels (e) – (h) for Subject 2 visually depict the Stokes number (St)-based projections of ideal droplet size ranges for maximal targeted deposition at the nasopharynx. The directional change of the St-projected ranges agree with the corresponding CFD-based ideal droplet size ranges in all the test cases, except in one trivial outlier: see panel (c), where the maximum ideal size limits for both 15 and 30 L/min are 24 μ m; the St-projected maximum ideal droplet size for 30 L/min is, however, 33.94 μ m. See Section 3.3 for a representative discussion for the data reported in (g).

improvement in nasopharyngeal delivery, by 2.215 orders-of-magnitude, with a standard deviation of 0.016 orders. Panel (b) in Fig. 9 plots the experimental measurements. Hence, the computational predictions differ from the *in vitro* data by less than 5%, thereby lending robust support to the implemented *in silico* framework.

313 4. Discussion

• On inputs to targeted drug design – With targeted delivery of pharmaceutic agents to the viral infection hot-spots in the posterior upper airway (e.g. at the nasopharynx)

Model	Simulation Case	Pearson's Correlation Coefficient (r)					p-value associated with correlation				
		PD 1	PD 2	PD 3	PD 4	PD 5	PD 1	PD 2	PD 3	PD 4	PD 5
Subject 1	Left Nostril Administration 15 L/min Inhalation	0.6805	0.6745	0.9176	0.6155	0.6620	2.53E-04	3.01E-04	2.78E-10	1.37E-03	4.26E-04
	Right Nostril Administration 15 L/min Inhalation	0.9526	0.8795	0.8469	0.8769	0.9580	7.43E-13	1.52E-08	1.80E-07	1.89E-08	2.01E-13
	Left Nostril Administration 30 L/min Inhalation	0.8191	0.6122	0.9725	0.5525	0.9577	9.87E-07	1.48E-03	2.07E-15	5.12E-03	2.22E-13
	Right Nostril Administration 30 L/min Inhalation	0.4607	0.7348	0.8711	0.5499	0.8029	2.35E-02	4.33E-05	3.06E-08	5.37E-03	2.34E-06
Subject 2	Left Nostril Administration 15 L/min Inhalation	0.9548	0.6513	0.7114	0.7296	0.9343	4.49E-13	5.66E-04	9.72E-05	5.21E-05	2.49E-11
	Right Nostril Administration 15 L/min Inhalation	0.9848	0.9629	0.9523	0.9805	0.9939	3.24E-18	5.29E-14	8.03E-13	4.77E-17	1.50E-22
	Left Nostril Administration 30 L/min Inhalation	0.9348	0.8904	0.5591	0.7557	0.8534	2.29E-11	5.66E-09	4.51E-03	1.95E-05	1.16E-07
	Right Nostril Administration 30 L/min Inhalation	0.9413	0.9512	0.9387	0.9877	0.9797	7.53E-12	1.02E-12	1.18E-11	3.05E-19	7.44E-17

Table 1: Statistical testing on the correlation between the regional deposition trends (for different drug droplet sizes) at the nasopharynx for the perturbed spray directions (i.e. PD 1-5), when compared to the nasopharyngeal deposition with the IU protocol.

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Figure 9: Panel (a) shows the order-of-magnitude IU-induced improvement in drug mass deposits at the nasopharynx of Subjects 1 and 2 (when compared to the CU delivery numbers), while considering the droplet size distribution in each administered shot of two common over-the-counter spray products: FlonaseTM and NasacortTM. Panel (b) shows the measurements from a set of physical experiments with sprayed watery solution in different Subject 3. As an indicator for agreement between the computational and experimental projections, the vertical range in (b) is a medial subset of that in (a). Note that several data-points roughly superimposed over each other, in both (a) and (b). Panel (c) presents a cartoon of the experimental setup. A separate in-set visual for the 3D-printed soft nose, with realistically pliable external nares, is shown in (d).

a clear challenge,^{15,40,41} the experimentally-validated findings (see Fig. 6) from this study point to the droplet size range of $\sim 6 - 14 \ \mu m$ as being the most effective at maximizing the sprayed and inhaled percentage deposition at the clinical upper airway target site for SARS-like infections. The information could be utilized to design next-generation intranasal drug formulations, along with novel spray devices and atomizers.

• On inputs for effective spray usage strategies – The significant 2 orders-of-magnitude improvement (see Fig. 9) in nasopharyngeal delivery of intranasally sprayed drugs with

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the new IU protocol, over the typically recommended CU protocol, clearly warrants a revisit of the standard usage instructions for existing nasal spray products. While Section 2.3 lays out the different criteria points for *in silico* detection of the IU direction[†]; in ordinary language: the user can replicate the IU protocol by holding spay nozzle as horizontally as possible at the nostril, with a slight tilt towards the cheeks and pointed a little at the outer edge of the eye (e.g., right eye if one is placing the spray at the right nostril). See Fig. 10 for a sample demonstration.

- On the limitations of respiratory flow modeling The reader should note that a 331 realistic modeling of mucociliary transport along the morphologically complex airway 332 cavity constitutes a significant open question in the domains respiratory transport 333 mechanics.⁴² In this study, we have implemented state-of-the-art algorithms to 334 identify the droplet sizes that are efficient at *direct* nasopharyngeal delivery, under 335 the impact of inhaled airflow when spraved into the intranasal space. However, a big 336 caveat lies in what happens to the larger droplets that happen to deposit along the 337 anterior parts of the airway. Quantifying their mucus-driven downstream transport 338 mechanics and correlating that with the therapeutic efficacy of the drug solutes when 339 they reach the posterior clinical target sites poses a major translational challenge, to 340 be addressed by the community in future. 341
- On the constraints posed by the reconstructed in silico geometries The CT-based • 342 anatomically realistic reconstructions, while accurately replicating the topological 343 convolutions implicit in a real tortuous respiratory cavity, still come with the caveat 344 of containing structurally rigid airway walls. However, though the rigidity of the walls 345 (intended to mimic the internal tissue surfaces and cartilages) is somewhat unrealistic, 346 the time-scale of inhaled transport is on the scale of 10^{-1} s.¹⁸ and the idealization 347 could be considered a mechanically feasible assumption that is sufficient to extract the 348 fundamental nuances underlying such physiologically complex transport processes. 349
- On the usability of the findings despite the small test cohort Clearly the current study 350 is somewhat limited given the restricted sample size of only two main test subjects 351 (i.e. Subjects 1 and 2). However, the congruity in targeted delivery improvement 352 (see Section 3.4 and Fig. 9) in a randomly-selected third subject (Subject 3) bodes 353 well for the general extensibility of the essential findings to a wider cohort. At the 354 least, the results presented here, though preliminary in essence given the small cohort 355 size, could be considered an important step in the mechanistic characterization of 356 the respiratory transmission dynamics for improving the performance of intranasally 357 administered spray products. 358
- On toxicity evaluation Any new formulation or drug delivery device that might attempt to replicate the improved targeted deposition at intranasal sites, based on the current findings, will essentially form a surface contacting mechanism with limited

† (i) Extended spray axis for the IU protocol intersects the nasopharynx; (ii) as a condition for clinical safety (based on recommendation from attending rhinologists^{15,37}), the axis must not cut through the septum; (iii) the spray axis should intersect the lateral wall of the nasal cavity as posteriorly as feasible.

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duration contact. For determination of usage safety levels, such a development will also require biocompatibility testing of the device, including check of three basic biocompatibility endpoints (i.e., cytotoxicity, irritation,⁴³ sensitization) per the Food and Drug Administration (FDA) guidance,^{44,45} by providing test data and/or relevant justification (e.g., history of clinical use for the same device).

³⁶⁷ 5. Final takeaways

Intranasal sprays could represent a useful ad-368 ministration strategy for nasal hygiene products, 369 prophylactics, and antivirals – for respiratory 370 pathogens that would first trigger an upper air-371 way infection, such as SARS-CoV-2. In this study, 372 we have used computational fluid dynamics simu-373 lations to illustrate that simple tweaks to the nasal 374 spray direction can result in vastly improved drug 375 delivery to the critical viral infection sites inside 376 the nose, more specifically the delivered dose reg-377 isters an approximately 2 orders-of-magnitude im-378 provement. The proposed IU protocol (see Figs. 3 379 and 4; also Fig. 10) is easy-to-replicate and has 380 been verified to be robust to small perturbations 381



Figure 10: Demonstrative sagittal sketch for the "Improved Use" (IU) protocol, outlining how to hold a spray bottle during intranasal administration. Illustration is by the lead author.

that may stem from user subjectivities. Also, the droplet size range of $\sim 6 - 14 \ \mu m$ is found most efficient at facilitating direct delivery of intranasally sprayed drug particulates at the nasopharynx, which is the dominant infection trigger zone. Both these key pieces of findings bear the promise for developing increasingly effective intranasal pharmaceutic formulations, along with upgraded designs for nasal drug delivery devices and atomizers.

388

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396 Author contributions

SB, DJM, AC conceived this study; SB developed the study protocol, the anatomic reconstructions and drafted the manuscript; MMHA carried out the physical experiments and the theoretical analysis; SB, YL, PAB, PA, NKK performed the numerical simulations; AM, ZS processed the computational data; JS tested the overthe-counter spray products; SB and DJM jointly supervised the student researchers (MMHA, YL, PAB, PA, NKK, AM, ZS).

403 Conflicts of interest

⁴⁰⁴ The authors declare no competing interests.

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